MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

Digitized by the Internet Archive
in 2015

https://archive.org/details/mountsinaijourna7020moun

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 70 NUMBER 1 JANUARY 2003

GERIATRICS

Barbara E.C. Paris and Carol F. Capello, guest editors

PART 1

CONTENTS

Introduction *Barbara E.C. Paris and Carol F. Capello* 1

The Biology of Aging *Bruce R. Troen* 3

Inflammatory Arthritis in the Elderly *Leslie Dubin Kerr* 23

Stroke in the Elderly *Mitchell S.V. Elkind* 27

Overview: Depression in the Elderly *Michael Serby and Mi Yu* 38

Review of Dementia *Micheline Dugué, Judith Neugroschl, Margaret Sewell, and Deborah Marin* 45

Urinary Incontinence in the Geriatric Population *Adam P. Klausner and Jonathan M. Vapnek* 54

Why Elder Abuse Continues to Elude the Health Care System *Fay S. Kahan and Barbara E.C. Paris* 62

Required Form for Authors C3

SAINT BARNABAS HEALTH CARE SYSTEM

LIBERTY HEALTHCARE SYSTEM, INC.

Veterans Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by the Mount Sinai Medical Center of New York and has the following affiliates: Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY; Saint Barnabas Health Care System, Livingston, NJ; Newark Beth Israel Medical Center, Newark, NJ; Liberty HealthCare System, Inc., Jersey City, NJ.

Editor-in-Chief

Sherman Kupfer, M.D.

Administrative Assistant

Ron Stein

Associate Editors

Harriet S. Gilbert, M.D.
Leslie A. Kuhn, M.D.
Philip S. Ledereich, M.D.

Assistant Editor for Housestaff

Leora Horwitz, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

Scott H. Barnett, M.D.
J. Hugh Baron, D.M.
David H. Bechhofer, Ph.D.
Constantin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
James L. Breen, M.D.
Donald Brief, M.D.
Daniel Buchbinder, D.M.D, M.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., M.P.H., M.P.P.
William H. Constad, M.D.
Joseph S. Eisenman, Ph.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Jack Hirschowitz, M.B., Ch.B.
Fred M. Jacobs, M.D., J.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M. Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkovitz, M.D.
Dana M. Lewis, M.L.S.
Tariq K. Malik, M.D., M.P.H.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Myron Miller, M.D.
Richard Panush, M.D.
Barbara E. C. Paris, M.D.
Jerome G. Porush, M.D.
Georges R. Ramalanjaona, M.D., D.Sc.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Tibor Rohacs, M.D.
Gregory J. Rokosz, D.O., J.D.
Joshua Rosenblatt, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Harry Schanzer, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Janet B. Serle, M.D.
Phyllis Shaw, Ph.D.
Scott H. Sicherer, M.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson N. Stone, M.D.
Max Sung, M.D.
Jules A. Titelbaum, M.D.
Thomas A. Ullman, M.D.
Richard P. Wedeen, M.D.
Klaudiusz R. Weiss, M.D.

Editorial Board

Barry S. Coller, M.D.
Panayotis G. Katsoyannis, Ph.D.
Jack G. Rabinowitz, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, Septemb October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-657 Subscription price: individuals (U.S. and Canada), $79 per year; libraries and institutions (U.S. and Canada), $121 per year; individuals (outs U.S. and Canada), $105 per year; libraries and institutions (outside U.S. and Canada), $147 per year. The charge per copy of a single numb issue is $25, for a two-number issue is $50. New subscriptions begin with the first issue of the calendar year. Send notice of change of addre 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send addre changes to *The Mount Sinai Journal of Medicine*, Box 1094. One East 100th Street, New York, NY 10029-6574. Telephone number (212) 24 6108. Fax (212) 722-6386. e-mail: msjournal@mssm.edu; web page: www.mssm.edu/msjournal. Copyright 2003

DISCLAIMER The statements and opinions expressed in *The Journal* by authors and contributors are solely their own and not those of The Mount S Medical Center or *The Mount Sinai Journal of Medicine*. All advertisements are expected to conform to ethical standards, and their appearance does not im endorsement or approval by The Mount Sinai Medical Center and/or *The Mount Sinai Journal of Medicine* of the products with respect to effectiveness, quality safety. The Mount Sinai Medical Center and *The Mount Sinai Journal of Medicine* do not hold themselves responsible for statements made by the authors contributors and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT Material printed in *The Journal* is protected by copyright. In accord with U.S. Copyright law, no part of *The Journal* may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior writte permission to do so. Permission should be requested from The Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574

Introduction

Barbara E.C. Paris, M.D., and Carol F. Capello, Ph.D.

It is certainly no secret that U.S. life expectancy has dramatically increased over the past century. We only have to look around us to see that our population is graying. Today, 35 million Americans are over 65 years old, and as the Baby Boomers age, this number will double in size and account for nearly one-quarter of our population (1). The oldest-old are growing in number at a particularly rapid rate. There will be approximately one million centenarians by the year 2050 (2).

This unprecedented shift in our society presents vast challenges to our health care system. For example, the elderly tend to under-report illness. They also display altered patterns and (often) more subtle manifestations of diseases, and respond differently to therapies than do their younger cohorts. Many factors contribute to this phenomenon, including impaired physiologic reserve and compromised homeostatic mechanisms.

Despite this, the Alliance for Aging Research notes that a majority of U.S. health care providers still have little or no specific education concerning caring for older adults. As Daniel Perry, Executive Director of the Alliance, points out (3), not all American health professionals need be certified in geriatric care, but all should receive at least "some formal exposure to geriatrics as part of their health education."

One of the missions of the Brookdale Department of Geriatrics and Adult Development at Mount Sinai is to be an educational resource — to improve the quality of life of older people through excellence in professional education. To ensure that health care providers have the formal training that they need to provide quality care for their older patients, the department has hosted several geriatrics conferences. For example, in the fall of 2001, more than 125 health care professionals attended our Geriatric Medicine Update and Board Review course on the Mount Sinai campus. The goal of the course was to update the health care community on the latest research and techniques in geriatrics, and to teach them how to apply this information in everyday practice.

The January and March 2003 issues of *The Mount Sinai Journal of Medicine* highlight selected presentations and workshops from this course and from clinical research in the department. Although a fairly narrow range of topics is covered in this issue, as a group they exemplify key areas of major concerns in health care today and address many of our fears related to growing old. The first article is an intellectually stimulating and comprehensive review of our current understanding of the biology of aging, providing an important backdrop for the subsequent topics presented.

For most of us, the potential loss of independence due to functional limitations, as can occur with arthritis and stroke, or with mental illness commonly due to depression and dementia, is frightening. Articles on these topics present up-to-date data related to the recognition of risk factors, screening modalities and early interventions for these illnesses — interventions that can improve quality of life and save health care dollars. Other problems, such as incontinence and elder abuse, are vastly underdiagnosed and sometimes considered taboo. We bring these important issues to the forefront in this journal, to help diminish the terrible isolation and withdrawal experienced by those who suffer from these problems. We have also in-

---

From the Henry L. Schwartz Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, One East 100th Street, New York, NY.

Address all correspondence to Barbara Paris, M.D., Department of Medicine, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn, NY 11219.

cluded an article on geriatric emergencies, since the emergency department is often the point of entry into the health care system for the elderly.

Finally, over the past century we have become quite proficient at prolonging life. We now are faced with many new questions about quality of life as we age, and it is our obligation to understand our patients' wishes for care at the end of life. Therefore, we have included an article that focuses on the perspective of the patient regarding this question.

This year marks the 21st anniversary of our department. In recognition of this effort, the *U.S. News and World Report* in 2002 has ranked Mount Sinai as being first in training in geriatric medicine among U.S. medical schools (4). We are honored by this distinction.

References

1. Daniel Perry (Executive Director of Alliance for Aging Research). Statement to Senate Special Committee on Aging. Feb 27, 2002. http://www.agingresearch.org/news_test_022802.cfm
2. Perls TT, Silver MH. Living to 100. New York: Basic Books; 1999.
3. Alliance for Aging Research. Alliance for Aging Research releases a new report highlighting the disconnect between the health needs of seniors and the training of health professionals [press release]. Feb 27, 2002. http://www.agingresearch.org/news/
4. Best graduate schools. U.S. News and World Report 2003 edition; http://www.usnews.com

Correction Notice

In the article "Percutaneous Stereotactic Radiofrequency Thermal Rhizotomy for the Treatment of Trigeminal Neuralgia," by Ernest S. Mathews and Steven J. Scrivani, in vol. 67(4): 288–299, Dr. Scrivani was erroneously listed as an M.D. His correct degrees are D.D.S., M.S. and D.M.Sc.

In our November issue, four errors were made in the Table of Contents:

- **History of Medical Professionalism**, by Rosemary Stevens, should be **Themes in the History of Medical Professionalism**
- **Professional Responsibility and the Virtues of a Physician**, by Edmund D. Pellegrino, should be **Professional, Profession and the Virtues of the Good Physician**
- **Panel Discussion** should be **Panel Discussion: Issues in Medical Ethics**
- **Index** should be **Author, Subject, Title Index to Volume 69**

The Biology of Aging

Bruce R. Troen, M.D.

Abstract

In humans, aging is inexorable. The progressive decrease in physiological capacity and the reduced ability to respond to environmental stresses lead to increased susceptibility and vulnerability to disease. Consequently, mortality due to all causes increases exponentially with aging. Attempts at understanding the causes of aging are limited by the complexity of the problem. Aging changes are manifest from the molecular to the organismic level; environmental factors affect experimental observations; secondary effects complicate elucidation of primary mechanisms; and precisely defined, easily measurable "biomarkers" are lacking. No one unifying theory may exist, since the mechanisms of aging could be quite distinct in different organisms, tissues, and cells. Evolutionary pressures have selected for successful reproduction, making it likely that the post-reproductive physiology of an organism (i.e., aging) is an epigenetic and pleiotropic manifestation of the optimization for early fitness. Indeed, antagonistic pleiotropy, wherein genes that enhance early survival and function but are disadvantageous later in life, may play an overriding role in aging. Theories of aging can be divided into two general categories: stochastic and developmental-genetic. These are not mutually exclusive, particularly when considering the free radical/mitochondrial DNA theory of aging. Increasing evidence suggests that cellular senescence and organismic aging are antagonistically pleiotropic manifestations of evolutionary pressures to prevent malignant transformation. In other words, aging may be the price we pay to avoid cancer. The beneficial paradox may be that the maximum lifespan potential of humans may have been achieved, in part, due to our ability to grow old.

Key Words: Aging, senescence, cellular, lifespan, mortality, antagonistic pleiotropy, cancer.

"Every day you get older — that's a law."
— *Butch Cassidy and the Sundance Kid* (1)

"There is no such thing as a free lunch."
— Anonymous (2)

"Aging seems to be the only available way to live a long life."
— Daniel Francois Esprit Auber (3)

Discussions of aging invariably begin by establishing satisfactory definitions for the term "aging" and the related word "senescence." Although the term "aging" is commonly used to refer to post-maturational processes that lead to diminished homeostasis and increased organismic vulnerability, the more correct term for this is "senescence." "Aging" can refer to any time-related process. In this paper, however, "senescence" and "aging" will be used interchangeably. "Normal" aging involves inexorable and universal physiological changes, whereas "usual" aging includes age-related diseases. For example, menopause and the decline in renal function represent aspects of normal aging. In contrast, coronary artery disease is an example of usual aging and is not found in all older persons. This approach to aging can utilize a conceptual framework that identifies intrinsic (developmental-genetic) versus extrinsic (stochastic) causes. However, accumulating evidence increasingly stresses the importance of both. Indeed, the altered homeostasis in older organisms is likely the result of a genetic program that determines the response to exogenous influences and thereby increases the predisposition to illness and death.

Lifespan and Life Expectancy

The average/median lifespan (also known as life expectancy) is represented by the age at

---

Associate Professor, Brookdale Department of Geriatrics and Adult Development, Bronx Veterans Administration Medical Center, Bronx, NY.

Address all correspondence to Bruce R. Troen, M.D., Miami Veterans Administration Medical Center - 11GRC, 1201 NW 16th Street, Miami, FL 33125.

This work is based on a presentation at the Geriatric Medicine Update and Board Review at the Mount Sinai School of Medicine, New York, NY on October 5–8, 2001, and upon the chapter "Cell and Molecular Aging," by Troen BR and Cristofalo VJ, in: Rosenthal RA, Zenilman ME, Katlic MR, editors. *Principles and Practice of Geriatric Surgery.* New York: Springer; 2001. pp. 8–23.

which 50% of a given population survive, and maximum lifespan potential (MLSP) represents the longest-lived member(s) of the population or species. The average lifespan of humans has increased dramatically over time, yet the MLSP has remained approximately constant and is usually stated to be 90–100 years (Fig. 1) (4). For 99% of our existence as a species, the average life expectancy for humans was very short compared to the present. Due to disease and accidents, people living 50,000 years ago rarely lived beyond the age of 40. Throughout most of recorded human history, socioeconomic status and nutritional status have been strongly associated with life expectancy and, along with disease, resulted in significant variations in the lifespan of individuals. By 1900, improved sanitation helped to raise the average life expectancy at birth in the United States to 57 years, but infectious disease was still a major killer. In the latter half of the twentieth century, better diet, health care, and reduced infant mortality had resulted in an average life expectancy in the United States of about 80 years as of 1980 (5). The increase in the average life expectancy has resulted in a compression of morbidity (a squaring of the mortality curve) toward the end of the lifespan (Fig. 1). The unavoidable presence of trauma and accidents prevents 100% survivability. Of note, the longest-lived human for whom documentation exists was Jeanne Calment, who died in France at the age of 122, in August 1997. The longest-lived male was Christian Mortensen, who died in San Francisco at the age of 115, in 1998. As causes of early mortality have been eliminated as a result of public health measures and improved medical care, more individuals have approached the maximum lifespan. Between 1960 and 1994, the population of those aged 85 and older increased by 274%. During this interval, the less elderly population doubled while the entire U.S. population increased by 45% (6).

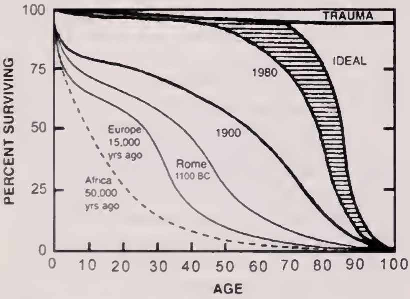

Fig. 1. Percent survival curve for humans at different times in history with varying environments, nutrition, and medical care. The 50% survival values have improved, but maximum lifespan potential has remained the same. Adapted with permission from: Cutler RG. Evolutionary perspective of human longevity. In: Hazzard WR, Andres R, Bierman EL, et al., editors. Principles of geriatric medicine and gerontology. New York: McGraw-Hill; 1990. p. 16 (reference 4).

MLSP appears to be species specific, implying a significant genetic component to the rate of aging. For example, humans have an MLSP 25–30-fold higher than mice. Some biodemographic estimates predict that elimination of most of the major killers such as cancer, cardiovascular disease, and diabetes would add no more than 10 years to the average life expectancy, but would not affect MLSP (7, 8). This implies an upper limit to the MLSP. Some models suggest that genes operate to raise or lower the relative risk of death, by making cancer, coronary disease, or Alzheimer's disease more likely, rather than by fixing the lifespan. One mathematical model predicts that if participants in the Framingham Heart Study had been able to maintain the levels of 11 different risk factors to be similar to those of a typical 30 year old, the men and women would have survived to an average age of 99.9 and 97.0 years, respectively (7).

There are three known regimens that can extend lifespan. The first two involve lowering ambient temperature and reducing activity, and are effective in poikilotherms (cold-blooded species). A decrease of 10%C or the elimination of a housefly's capacity to fly extends the maximum lifespan approximately 250% (9). Both of these manipulations decrease the metabolic rate and are accompanied by decreases in free radical generation and oxidative damage to protein and DNA. Dietary restriction without malnutrition can increase both the average and maximum lifespans of mice and rats by more than 50% (10, 11). Although calories are severely restricted (up to 40%), essential nutrients such as vitamins and minerals are maintained at levels equivalent to those found in *ad libitum* diets. The diet-restricted animals also exhibit a delay in the onset of physiological and pathological changes associated with aging (12). These include hormone and lipid levels, female reproduction, immune function, nephropathy, cardiomyopathy, osteodystrophy, and malignancies. Size, weight, fat percentage and some organ weights are markedly less in calorically restricted animals (13). The specific metabolic rate, the amount of oxygen consumed per gram of tissue, decreased in rats subjected to caloric restriction (14, 15). However in one study, long-term food restriction did not alter the metabolic rate (16). This finding suggests that the specific metabolic rate may not be a critical determinant of longevity. To date, the effect of dietary restriction on lifespan has been convincingly demonstrated only in rodents. Caloric restriction in rhesus monkeys leads to reductions in body temperature and energy expenditure, consistent with changes seen in rodent studies in which aging is retarded by dietary restriction (17, 18). Calorie restriction also increases high-density lipoprotein (19) and retards the post-maturational decline in serum dehydroepiandrosterone sulfate in the rhesus monkeys (20).

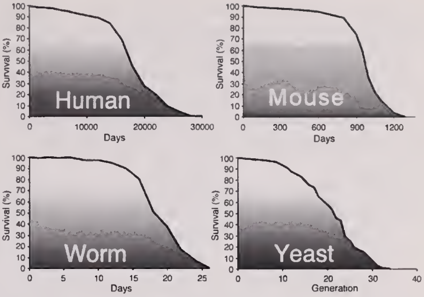

Fig. 2. Viability curves from different model organisms have a similar characteristic shape. Representative mortality data are shown for *Homo sapiens*, *Mus musculus*, *Caenorhabditis elegans*, and *Saccharomyces cerevisiae*. Reproduced with permission from reference 23.

Characteristics of Aging

There is evidence supporting at least 5 common characteristics of aging in mammals (Table 1):

1. **Increased mortality with age after maturation.** In the early nineteenth century, Gompertz first described the exponential increase in mortality with aging due to various causes, a phenomenon that still pertains today (21). In 1995, the death rate for all causes for people in the U.S. between the ages of 25–44 was 189.5/100,000 and for those aged 65 and over was 5,069.0/100,000: a >25-fold increase (22). Indeed, the pattern of age-related survival is similar across species, including invertebrates and single-cell organisms (Fig. 2) (23).

2. **Changes in biochemical composition in tissues with age.** There are notable age-related decreases in lean body mass and total bone mass in humans (24, 25). Although the amount of subcutaneous fat is either unchanged or decreases, total fat remains the same (24). Consequently, the percentage of adipose tissue increases with age. At the cellular level, many markers of aging have been described in various tissues from different organisms (26). Two of the first to be described were increases in lipofuscin (age pigment) (27) and increased cross-linking in extracellular matrix molecules such as collagen (28, 29). Additional examples include age-related changes in both the rates of transcription of specific genes and the rate of protein synthesis and numerous age-related alterations in post-translational protein modifications, such as glycation and oxidation (30, 31).

3. **Progressive decrease in physiological capacity with age.** Many physiologic changes have been documented in both cross-sectional and longitudinal studies. Examples include declines in glomerular filtration rate, maximal heart rate, and vital capacity (32). These decreases occur linearly from about the age of 30; however, the rate of physiological decline is quite heterogeneous from organ to organ and individual to individual (33, 34).

4. **Reduced ability to respond adaptively to environmental stimuli with age.** A fundamental feature of senescence is the diminished ability to maintain homeostasis (35). This is manifest not primarily by changes in resting or basal parameters, but in the altered response to an external stimulus such

TABLE 1
Characteristics of Aging

1.	Increased mortality with age after maturation.
2.	Changes in biochemical composition in tissues with age.
3.	Progressive decrease in physiological capacity with age.
4.	Reduced ability to respond adaptively to environmental stimuli with age.
5.	Increased susceptibility and vulnerability to disease.

as exercise or fasting. The loss of "reserve" can result in blunted maximum responses as well as in delays in reaching peak levels and in returning to basal levels. For example, the induction of hepatic tyrosine aminotransferase activity by fasting is both attenuated and delayed in old rodents (35).

5. **Increased susceptibility and vulnerability to disease.** The incidence and mortality rates for many diseases increase with age and parallel the exponential increase in mortality with age (36). For the five leading causes of death for people over 65, the relative increase in death rates compared to the rates for people age 25–44 are: heart disease 92-fold, cancer 43-fold, stroke greater than 100-fold, chronic lung disease greater than 100-fold, and pneumonia and influenza 89-fold (22). The basis for these dramatic rises in mortality is incompletely understood, but presumably involves changes in the function of many types of cells, which lead to tissue/organ dysfunction and systemic illness. Interestingly, a retrospective study of centenarians demonstrated that they live 90–95% of their lives in very good health and with a high level of functional independence (37). The centenarians do suffer a 30–50% annual mortality at the end of their lives, but this represents a marked compression of morbidity toward the end of life and is close to the idealized survival curve in Fig. 1.

Mechanisms / Causes of Aging

Evolutionary

In an effort to adequately explain the phenotype of aged organisms, many theories about the cause(s) of aging have been proposed. However, what is supposedly "known" about the fundamental molecular mechanisms involved in aging remains controversial and largely unproven. A major reason for this is the obvious complexity of the problem. Aging changes are manifest from the molecular to the organismic levels; environmental factors affect experimental observations; secondary effects complicate elucidation of primary mechanisms; and precisely defined, easily measurable "biomarkers" are lacking. No one unifying theory may be valid, since the mechanisms of aging could be quite distinct in different organisms, tissues, and cells.

A general framework for a plausible theory of aging begins with understanding the evolutionary basis of senescence. Evolutionary pressures select for a minimum successful life: this includes the ability to reach reproductive age, procreate, and then care for offspring until they are weaned (so that they, in turn, will achieve reproductive age and continue the cycle) (38, 39). Within this context, it is likely that the post-reproductive/parental physiology of an organism is an epigenetic and pleiotropic manifestation of the optimization for early fitness. Kirkwood proposes that three categories of genes may be involved in senescence (40): (a) those that regulate somatic maintenance and repair, (b) negatively pleiotropic genes that enhance early survival but are disadvantageous later in life (antagonistic pleiotropy), and (c) harmful late-acting mutations upon which little evolutionary selection is exerted. The presence of these genes may represent a spectrum from general to species specific (Fig. 3). Genes involved in cell maintenance and repair are likely to be present in all (or most) organisms, since such essential processes are similar across species. Late-acting mutations are probably species specific, because they are likely to be individualistic and random. Non-maintenance pleiotropic genes could be universally found within a population or species, but may not be shared between species. An example of antagonistic pleiotropy would be the high expression of testosterone in a male gorilla, which could lead to increased aggression and strength that would allow the male to become dominant and mate more frequently, but may eventually lead to a shortened lifespan due to increased atherosclerosis. Recent studies at the molecular genetic level have suggested that cellular senescence may be antagonistically pleiotropic because it prevents tumorigenesis, but also contributes to organismic aging (see below).

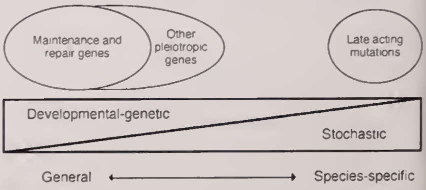

Fig. 3. Genes / events regulating longevity and senescence. Adapted with permission from: Kirkwood TB. Human senescence. Bioessays 1996; 18:1009–1016 (reference 40).

Historically, theories of aging have been divided into two general categories: stochastic and developmental-genetic (Table 2). The term "developmental-genetic" implies a more active genetic control of senescence than likely exists (see above). In addition, as described below, these categories are not mutually exclusive, particularly when considering the free radical/mitochondrial DNA theory of aging. Indeed, there is probably a spectrum from birth to senescence that reflects a decreasing influence of active genetic influences and an increasing effect of stochastic events (Fig. 3). This would parallel the shift in importance from general to species-specific genes.

Stochastic Theories

Somatic Mutation and DNA Repair

Stochastic theories propose that aging is caused by random damage to vital molecules. The damage eventually accumulates to a level sufficient to result in the physiological decline associated with aging. The most prominent example is the somatic mutation theory of aging, which states that genetic damage from background radiation produces mutations that lead to functional failure and, ultimately, death (41, 42). Exposure to ionizing radiation does shorten lifespan (43). However, analysis of survival curves of radiation-treated rodent populations reveals an increase in the initial mortality rate without an effect on the subsequent rate of aging (44). The lifespan shortening is probably due to increased cancer and glomerulosclerosis rather than accelerated aging *per se* (45).

The DNA repair theory is a more specific example of the somatic mutation theory. The ability to repair ultraviolet-radiation-induced DNA damage in cell cultures derived from species with a variety of different lifespans correlates directly with the MLSP (46). Unfortunately, there is not enough experimental support to conclude that these differences between species are a causative factor in aging. The cumulative evidence indicates that overall DNA repair capacity does not appear to change with age, although the site-specific repair of select regions of DNA appears to be important in several types of terminally differentiated cells (47). Future studies will need to focus upon repair rates of specific genes rather than indirect general measurements.

TABLE 2
Theories of Aging

- **Stochastic**
  - Somatic Mutation and DNA Repair
  - Error-Catastrophe
  - Protein Modification
  - Free Radical (Oxidative Stress) / Mitochondrial DNA
- **Developmental-Genetic**
  - Longevity Genes
  - Accelerated Aging Syndromes
  - Neuroendocrine
  - Immunologic
  - Cellular Senescence
  - Cell Death

Error-Catastrophe

The error-catastrophe theory proposes that random errors in synthesis eventually occur in proteins that synthesize DNA or other "template" molecules (48). Generally, errors occurring in proteins are lost by natural turnover and simply replaced with error-free molecules. Error-containing molecules which are involved in the protein-synthesizing machinery, however, would introduce errors into the molecules that they produce. This could result in an amplification such that the subsequent rapid accumulation of error-containing molecules would result in an "error-catastrophe" that would be incompatible with normal function and life. However, although there are numerous reports of altered proteins in aging, no direct evidence of age-dependent protein mis-synthesis has yet been reported. The altered proteins that do occur in aging cells and tissues are, instead, due to post-translational modifications such as oxidation and glycation (49, 50). The increases in altered proteins appear to be due to decreased clearance in older cells (51).

Protein Modification

In addition to age-related changes in the steady-state levels of proteins, qualitative alterations leading to changes in function occur. Aging is accompanied by decreased specific activity in many enzymes, altered heat stability, and increased carbonyl content of proteins (50). These changes can be caused by direct oxidation of amino acid residues, metal-catalyzed oxidation, modification by lipid oxidation products, and glycation. Kohn (29) and Bjorksten (28) hypothesized that the accumulation of post-translationally altered proteins could impair cellular, and ultimately, organ function. Although collagen undergoes increased cross-linking with age (52), such alterations can lead to improved function at some sites and to impaired function at others (53). The nonenzymatic reaction of carbohydrates with amino groups of proteins (glycation) can give rise to advanced glycosylation end-products (AGEs) (50). These AGEs increase with aging and are implicated in diabetes, eye disorders, and amyloid accumulation. Many extracellular matrix proteins exhibit increased cross-linking with age. Proper organ function depends upon a normal extracellular matrix for processes such as diffusion of essential molecules. In addition, the extracellular matrix plays an important role in the regulation of gene expression. The cross-linking of macromolecules such as collagen, elastin, osteocalcin, and the eye lens protein crystallin (which may be responsible for cataract formation in both the diabetic and aged lens) could alter both of these processes. These covalent protein-protein interactions probably play a role in the increased stiffness of vascular walls with aging. Protein carboxyl methyltransferase (PCMT) assists in the repair of spontaneously arising atypical protein isoaspartyl residues (54). Overexpression of PCMT at 29°C in flies extended lifespan, suggesting that under certain environmental conditions, protein repair could be important in longevity.

Free Radical (Oxidative Stress) / Mitochondrial DNA

Another potential cause of cross-linking — free radicals — forms the basis for a theory that has elements of both the stochastic and developmental-genetic classes. Harman initially proposed that most aging changes are due to molecular damage caused by free radicals (55, 56), which are atoms or molecules that contain an unpaired electron and are therefore highly reactive. Aerobic metabolism generates the superoxide radical ($O_2^{\bullet -}$), which is metabolized by superoxide dismutases to form hydrogen peroxide (H_2O_2) and oxygen (57). Hydrogen peroxide can go on to form the extremely reactive hydroxyl radical (OH•). These oxygen-derived species can react with macromolecules in a self-perpetuating manner; they create free radicals out of subsequently attacked molecules, which in turn create free radicals out of other molecules, thereby amplifying the effect of the initial free radical attack (9). Reactive oxygen species appear to play a role in regulating differential gene expression, cell replication, differentiation, and apoptotic cell death (in part by acting as secondary messengers in signal transduction pathways) (58, 59). Production of free radicals in the heart, kidney, and liver of a group of mammals was found to be inversely proportional to the maximum lifespan, although the activities of individual anti-oxidative enzymes were not consistently related to maximum lifespan (60). Overexpression of either superoxide dismutase or catalase alone in transgenic flies does not extend lifespan (61), but some transgenic flies with increased expression of both Cu, Zn-superoxide dismutase and catalase, which act in tandem to remove $O_2^{\bullet -}$ and H_2O_2, respectively, exhibit up to a one-third extension of average and maximum lifespan (61). In addition, there was increased resistance to oxidative damage and an increase in the metabolic potential (total amount of oxygen consumed during adult life per unit body weight).

The mitochondrial DNA / oxidative stress hypothesis represents a synthesis of several theories and therefore comprises elements of both stochastic and developmental-genetic mechanisms of aging (see below). It is proposed that reactive oxygen species contribute significantly to the somatic accumulation of mitochondrial DNA mutations, leading to the gradual loss of bioenergetic capacity and eventually resulting in aging and cell death (Fig. 4) (62–64). Ozawa has dubbed this the "redox mechanism of mitochondrial aging" (65). Mitochondrial DNA (mtDNA) undergoes a progressive age-related increase in oxygen free radical damage in skeletal muscle (66–68), the diaphragm (69, 70), cardiac muscle (71–74), and the brain (75, 76). This exponential increase in damage correlates with the increase in both point and deletional somatic mtDNA mutations seen with age. Interestingly, extrapolation of the curve to the point where 100% of cardiac mtDNA exhibits deletion mutations produces an age of 129 (65). A deleterious positive feedback results, wherein mtDNA damage leads to defective mitochondrial respiration, which in turn enhances oxygen free radical formation, leading to additional mtDNA damage. Mitochondrial DNA is maternally transmitted, continues to replicate throughout the lifespan of an organism in both proliferating and post-mitotic (non-proliferating) cells, and is subject to a much higher mutation rate than nuclear DNA. This is due, in large part, to inefficient repair mechanisms and its proximity to the mitochondrial membrane

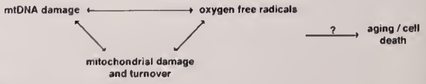

Fig. 4. Mitochondrial DNA and free radical interaction.

where reactive-oxygen species are generated. Defects in mitochondrial respiration with age are found not only in normal tissues (77), but also in people with diseases that are increasingly manifest with age, such as Parkinson's disease (78, 79), Alzheimer's disease (80, 81), Huntington's chorea (82), and other movement disorders (83). Diseases for which mtDNA mutations have been found include Alzheimer's (84, 85) and Parkinson's diseases (75, 85–88), and a large number of skeletal and cardiac myopathies (69, 89–93). Apoptosis has also been associated with mtDNA fragmentation (94). Is the phenotype of aging in tissues actually due to mtDNA mutation? Specific mutations, while increasing with age, seldom account for more than several percent of the total mtDNA. However, some studies suggest that the total percentage of mtDNA affected by mutations is much greater, as much as 85%, and increases with age (65). In addition, caloric restriction in mice retards the age-associated accumulation of mtDNA mutations (95). Inherited mitochondrial DNA variants are associated with aging and longevity (96). The J haplogroup was found in a significantly greater percentage of male centenarians in northern Italy than in younger subjects. Interestingly, this same mitochondrial haplotype is overrepresented in a number of complex diseases (97), raising the possibility of an antagonistically pleiotropic gene or genes that exert deleterious effects in younger individuals, but lead to better health at later ages (successful aging). To complicate matters further, mitochondrial DNA polymorphisms are present in different frequencies in various aged populations from Italy, Ireland, and Japan (98). Ongoing studies in Utah, utilizing extensive genealogical records of Mormons, are testing the hypothesis that longevity is maternally determined, given the inheritance of only maternal mtDNA.

Agents that bypass blocks in the respiratory chain, such as coenzyme Q10, tocopherol, nicotinamide, and ascorbic acid, would be predicted to ameliorate some of the effects of mitochondrial disease and aging. Withdrawal of coenzyme Q from the diet of nematodes extends their lifespan by approximately 60% (99). Caloric restriction, which can extend lifespan, reduces oxidative damage in primates (100). There are epidemiological studies that suggest roles for dietary antioxidants in the reduction of vascular dementia, cardiovascular disease, and cancer in humans (101). However, results to date in treatment of patients with myopathies have been variably or only anecdotally successful (65). This suggests that a complex interaction exists between pro-oxidant and antioxidant forces in the cell, and that regulation of the balance between the two may be the critical determinant in mitochondrial, and subsequently, cellular and tissue integrity during aging.

Developmental-Genetic Theories

Developmental-genetic theories consider the process of aging to be part of the genetically programmed and controlled continuum of development and maturation. Although this is an attractive notion, the diverse expression of aging effects is in sharp contrast to the tightly controlled and very precise processes of development. Also, evolution selects for the optimization of reproduction; the effects of genes expressed in later life probably do not play a large role in the evolution of a species. This class of theories is supported by the observation that the maximum lifespan is highly species specific. As noted above, the maximum lifespan for humans is 30 times that of mice. In addition, studies comparing the longevity of monozygotic and dizygotic twins and non-twin siblings have shown a remarkable similarity between monozygotic twins that is not seen in the other two groups.

Longevity Genes

There is ample evidence in many species that MLSP is under genetic control, though the degree of heritability is likely to be less than 35% (102). Despite this apparently low figure, genetic mutations can significantly modify senescence. In yeast a number of genes affect both the average and maximum lifespan (103). The products of these genes act in diverse ways, including modulating stress response, sensing nutritional status, increasing metabolic capacity, and silencing genes that promote aging. In the nematode (*Caenorhabditis elegans*), mutants with increased lifespan have revealed various genes that appear to play a relevant role (104): *age*-1 alters aging rate; *daf*-2 and *daf*-23 activate a delay in development; *spe*-26 reduces fertility; and *clk*-1 alters the biological clock. These genes alter stress resistance (particularly in response to ultraviolet light), development, signal transduction, and metabolic activity. The recently isolated *daf*-2 gene appears to encode an insulin-receptor family member (105). Mutations in *daf*-2 can double the lifespan, but require the *daf*-16 gene (106). A mutation in the *daf*-16 gene suppresses the UV resistance and increases longevity of the other gene mutants, suggesting that it acts at a critical point downstream of the other genes (104). The *daf*-16 gene is a member of the hepatocyte nuclear factor-3/forkhead family of transcriptional regulators, involved in a variety of signal transduction pathways, including insulin signaling (107). A notable connection between single gene effects upon aging in yeast and higher eukaryotes was revealed by the finding that overexpression of the *SIR2* gene and its homolog extend lifespan in yeast and nematodes, respectively (23). Despite acting via different mechanisms, *SIR2* and its homolog may both exert their effects by linking the regulation of metabolic rate to aging.

A line of *Drosophila melanogaster* has been identified that exhibits an approximately 35% increase in average lifespan and enhanced resistance to various forms of stress, including starvation, high temperature, and dietary paraquat, a free-radical generator (108). The mutation responsible, dubbed "Methuselah," appears to reside within a single gene that is homologous to GTP-binding transmembrane domain receptors. Another single gene mutation leads to an almost doubling of the average adult *Drosophila* lifespan without a decline in fertility or physical activity (109). This gene, named "Indy" (for "I'm not dead yet"), is homologous to a mammalian sodium dicarboxylate cotransporter, which is a membrane protein that transports Krebs cycle intermediates. The investigators speculate that the mutation in the Indy gene may create a metabolic state that mimics caloric restriction. Previous studies have demonstrated that one group of long-lived flies is more resistant to oxidative stress (110), whereas another group exhibits resistance to starvation and desiccation (111).

Genetic analysis of longevity in mammals has not been as revealing. However, immune loci in mice and humans have been implicated in long-lived subjects (103) (see below). In addition, in the gene encoding the signaling molecule p66(shc), there is a mutation which significantly enhances the resistance to oxidative stress and increases the mean lifespan of mice by 30% (112). The Snell dwarf mouse contains a single gene mutation that alters pituitary development and prevents the production of growth hormone, thyrotropin, and prolactin (113). The dwarf mouse also exhibits an extended lifespan of 25–50%, but is much smaller than normal mice. In contrast, the mice with the mutant p66 develop normally and are not significantly smaller than wild type mice. As noted above, a number of mitochondrial DNA polymorphisms are associated with longevity. In addition, the epsilon 4 allele of apolipoprotein E (ApoE), which is associated with increased coronary disease and Alzheimer's disease, is inversely correlated with longevity (114). In contrast, the epsilon 2 allele of ApoE and an angiotensin-converting enzyme (ACE) allele are found more frequently in French centenarians (114). Interestingly, the ApoE2 allele is associated with type III and IV hyperlipidemia, and the ACE allele predisposes to coronary disease. These findings further suggest that genes can exert pleiotropic age-dependent effects upon longevity. Perls et al. note that support for a genetic contribution to human longevity is further provided by data demonstrating that siblings and parents of centenarians live longer (115). Linkage analysis implicates the presence of a gene or genes on chromosome 4 that are associated with exceptional longevity (115). These authors report that a high percentage of centenarians have had children while in their 40s (well before assisted reproduction). They therefore postulate that an evolutionary force to prolong the period of child bearing would lead to the selection of longevity-enabling genes. Collectively, these studies also raise the question as to whether some genes affect susceptibility to disease rather than alter intrinsic aging.

In contrast to studies that uncover alterations in the expression of single genes during aging, Weindruch and Prolla and their colleagues have begun investigating the broad spectrum of changes in gene expression that occur during aging and calorie restriction in mice and in monkeys (116–119). A common theme is that aging induces a differential gene expression pattern in muscle and brain consistent with inflammatory and oxidative stress, and reduced expression of metabolic and biosynthetic genes. In muscle and brain from mice, caloric restriction either completely or partially prevented the age-related changes in gene expression. Interestingly, caloric restriction did not ameliorate the age-induced alteration in the program of gene expression seen in muscle from aging monkeys. So even though the age-related changes in gene expression may be similar across species, the response to caloric restriction may not be similar.

Accelerated Aging Syndromes

Although no genetic disease exists that is an exact phenocopy of normal aging, several human genetic diseases, including Hutchinson-Gilford syndrome (the "classic" early-onset progeria seen in children), Werner's syndrome ("adult" progeria), and Down's syndrome (trisomy 21), display some features of accelerated aging (120).

Werner's syndrome (WS) is an autosomally recessive inherited disease (121). Patients prematurely develop arteriosclerosis, glucose intolerance, osteoporosis, early graying, loss of hair, skin atrophy, and menopause. However, they do not typically suffer from Alzheimer's disease or hypertension. WS patients have an increased incidence of sarcomatous tumors and develop cataracts on the posterior surface of the lens, not in the nucleus, as is usually seen in older people. In addition, they develop laryngeal atrophy and ulcerations on the arm and legs. Most patients die before the age of 50. The gene responsible for WS has been localized to chromosome 8 (122) and appears to be a helicase (123), an enzyme involved in unwinding DNA. DNA helicases play a role in DNA replication and repair. Cells from WS patients display chromosomal instability, elevated rates of gene mutation, and nonhomologous recombination. However, there is no obvious defect in DNA repair mechanisms, as evidenced by a resistance to ultraviolet exposure or other DNA damaging agents, similar to normal cells.

Hutchinson-Gilford syndrome is an extremely rare, autosomal recessive disease in which aging characteristics begin to develop within several years of birth (121). These include wrinkled skin, stooped posture, and growth retardation. These patients suffer from advanced atherosclerosis, and usually die from myocardial infarction, by the age of 30. However, unlike WS patients, they do not typically suffer from cataracts, glucose intolerance, or skin ulcers.

People with Down's syndrome have trisomy or a translocation involving chromosome 21 (120, 121). They suffer from the early onset of vascular disease, glucose intolerance, hair loss, and degenerative bone and joint disease, as well as increased incidence of cancer. Their lifespan is apparently 50–70 years (not as short as previously believed, since earlier mortality may have represented neglect of these individuals). Dementia occurs earlier and more often in patients with Down's syndrome than in the general population. Patients develop neuropathological changes similar to the changes seen in dementia of Alzheimer's type, including amyloid deposition and neurofibrillary tangles. This may be related to the presence of the ß-amyloid gene on chromosome 21.

Kuro-o recently reviewed a number of mouse models which have been developed that exhibit many of the aging phenotypes seen in humans (124) (Table 3). Of these, the *klotho* mouse suffers from a defect in a single gene that codes for a membrane protein; it exhibits a plethora of marked age-related phenotypes that are also seen in humans. These include reduced lifespan, decreased activity, premature thymic involution, skin atrophy, arteriosclerosis, osteoporosis, emphysema, and lipodystrophy. There are a number of strains of senescence-accelerated mice (SAM) that exhibit variable aging phenotypes consistent with multigenic effects. Targeted disruption of genes responsible for premature aging syndromes in humans results in incomplete or absent age-related phenotypes. Despite the fact that none of the mouse models displays all of the phenotypes associated with human aging, they are likely to be valuable tools in identifying some of the molecular mechanisms of aging.

Neuroendocrine Theory

The neuroendocrine theory proposes that functional decrements in neurons and their associated hormones are central to the aging process (125). An important version of this theory holds that the hypothalamic-pituitary-adrenal (HPA) axis is the master regulator of aging in an organism. Because the neuroendocrine system regulates early development, growth, puberty, control of the reproductive system, metabolism, and many other aspects of normal physiology, functional changes in this system could exert effects throughout the organism. The decline in female reproductive capacity is an obvious neuroendocrine age-related change. Mounting evidence suggests that both the ovary and the brain play key roles in menopause (rather than the previously held view of ovarian exhaustion) (126). The neuroendocrine theory of aging is supported by experiments that show that hypophysectomy, followed by the replacement of known hormones, maintains (and may extend) lifespan in rodents (127). In addition, reductions in brain dopaminergic neurotransmission are more prominent in a shorter-lived rat strain (128). Levodopa, a dopaminergic drug, can prolong the mean lifespan in mice (129). Treatment of rats with deprenyl facilitates the activity of the nigrostriatal dopaminergic neurons and protects these neurons from their age-related decay (130), and de-

TABLE 3
Mouse Models for Human Aging

Model	Similarities to human aging	Lifespan and onset of aging	Differences from human aging	Genetics
Kl$^{-/-}$	Shortened lifespan, infertility, growth retardation, decreased spontaneous activity, premature thymic involution, ectopic calcification, skin atrophy, arteriosclerosis, osteoporosis, pulmonary emphysema, lipodystrophy	Average lifespan: ~9 weeks Onset of aging: ~4 weeks	Phenotypes not observed: neoplasms, cataracts, diabetes mellitus, brain atrophy	Loss of function mutations in the *klotho* gene (a single-pass membrane protein with homology to beta-glucosidase)
Sam	Amyloidosis, neoplasms, hyperinflation of the lung, hearing impairment, osteoporosis, defects in learning and memory, cataracts, brain atrophy	Average lifespan: ~10 months Onset of aging: < 8 months	Aging phenotypes are distributed among various SAMP strains	Not determined
WRN$^{-/-}$	Premature loss of proliferative capacity in fibroblasts, sensitivity to topoisomerase inhibitors	Not reported	Mutant mice are apparently normal	Targeted disruption of the Werner syndrome gene (RecQ-like DNA helicase)
CSA$^{-/-}$ *CSB*$^{-/-}$	Growth retardation, neurological defects	Almost normal lifespan	Other age-related phenotypes are not observed/examined	Targeted disruption of the Cockayne's syndrome group A (*CSA*) or group B (*CSB*) gene (DNA helicase)
Atm$^{-/-}$	Growth retardation, neurological dysfunction, infertility, malignant thymic lymphoma, sensitivity to X-ray irradiation	Develop thymic lymphoma before 4.5 months of age	Other age-related phenotypes are not observed or not examined	Targeted disruption of the *ATM* gene (a nuclear protein with PI-3-kinase-like domain)
mTR	Infertility, graying of the hair, alopecia, skin lesions, impaired stress response, impaired proliferation of hematopoietic cells, neoplasms, delayed wound healing	Average lifespan: 18 months in the 6th generation	Aging phenotypes appear only in late-generation telomerase-deficient mice with extremely shortened telomeres. Phenotypes not observed: arteriosclerosis, osteoporosis, cataracts, diabetes mellitus, etc.	Targeted disruption of the gene for the telomerase RNA component
Over expression of growth hormone	Scoliosis, weight loss, decline or reproductive capacity, insulin resistance, astrogliosis in the brain, glomerulonephritis, glomerulosclerosis, reduced replicative potential of fibroblasts	Lifespan: <50% of controls Onset of symptoms: 6–8 months of age	Growth hormone levels decline with age in humans and in experimental animals	Overexpression of rat, bovine, ovine or human growth hormone under the control of the metallothionein or phosphoenolpyruvate carboxykinase promoters

Reproduced with permission from Kuro-o M. Disease model: human aging. Trends Mol Med 2001; 7:179–181 (reference 124).

prenyl increases both the average and maximum lifespan (131, 132). Many human studies demonstrate gradually decreasing levels of peripheral hormones accompanied by normal levels of trophic hormones (125). This suggests either increased response to the peripheral hormones by the HPA axis or inappropriately low expression of the stimulating hormone. However, many organisms with aging phenotypes similar to those of higher vertebrates lack complex neuroendocrine systems. The changes that occur in the neuroendocrine system may be due to fundamental age-related changes in all cells and may therefore be secondary manifestations of the aging phenotype.

Immunologic Theory

The immunologic theory of aging is based upon two main observations: (a) the functional capacity of the immune system declines with age, as evidenced by a decreased response of T cells to mitogens and reduced resistance to infectious disease; and (b) autoimmune phenomena increase with age, such as an increase in serum autoantibodies (133). There is a shift toward increasing proportions of memory T cells, accompanied by enhanced expression of the multidrug-resistance p-glycoprotein (134). Humoral (B-cell mediated) immunity also declines with age, as evidenced by decreased antibody production and a disproportionate loss in the ability to make high affinity IgG and IgA (immunoglobulin G and A) antibodies. In addition, differences in the MLSP of different strains of mice have been related to specific alleles in the major histocompatibility gene complex (135). The genes in this region also contribute to the regulation of mixed-function oxidases (P-450 system), DNA repair, and free-radical-scavenging enzymes. Caruso et al. suggest that mouse and human histocompatibility genes may be associated with longevity via different mechanisms, in mice via susceptibility to lymphomas and in humans via infectious disease susceptibility (136). There is also evidence that cytokine gene polymorphisms may interact with histocompatibility genes to influence longevity (136). Although the immune system obviously plays a central role in health maintenance and survival, similar criticism can be directed at the immunologic theory as has been directed at the neuroendocrine theory. Complex immune systems are not present in organisms that share aspects of aging with higher organisms. In addition, the inability to distinguish between fundamental changes occurring in many types of cells and tissues, not just those of the immune system, and the secondary effects mediated by the aging-altered immune system, make interpretation of this theory difficult. Proposed mechanistic studies of the immune theory include producing transgenic mice that carry the histocompatibility complex from a longer-lived rodent species, to determine effects on disease incidence and lifespan.

Cellular Senescence

The complexity of studying aging in organisms has led to the use of well-defined cell culture systems as models for cellular aging or senescence. Hayflick and Moorhead (137) pioneered the model of replicative senescence and identified normal human diploid fibroblasts in culture as a model for aging. They observed an initial period of rapid and vigorous proliferation, invariably followed by a decline in growth rate and proliferative activity, finally leading to a cessation of proliferation. This model proposed that aging is a cellular as well as an organismic phenomenon, and that the loss of functional capacity of the individual reflected the summation of the loss of critical functional capacities of individual cells. It is important to note that populations of senescent cells do not necessarily die, and that they can be maintained in culture for years in a post-mitotic (non-proliferating) state, with regular changes of culture medium (138–140). The loss of proliferative capacity of human cells in culture is intrinsic to the cells and not dependent upon environmental or culture conditions (137). In addition, senescence is inevitable unless the cells undergo transformation and acquire a constellation of abnormal characteristics such as multiple chromosomal abnormalities, genetic mutations, and changes in morphology and growth rate. The number of times the cells divide is also more important in determining proliferative lifespan than the actual time the cells spend in culture (141). Cells continuously passaged in culture until the end of their proliferative lifespan achieve approximately the same number of population doublings (PDLs) as cells that are held in a stationary phase for an extended period (months) and then recultured until senescence. The cells therefore seem to possess an intrinsic mechanism that "counts" the number of divisions and not the time that passes.

In addition to studies on fibroblasts, limited *in vitro* lifespan has been reported for glial cells (142), keratinocytes (143), vascular smooth muscle cells (144), lens cells (145), endothelial cells (146), and lymphocytes (147). *In vivo*, serial transplants of normal somatic tissues, such as skin and breast, from old donor mice to young genetically identical recipients show a decline in proliferative activity and eventual failure of the graft (148). Similarly, skin from old donors retained an increased susceptibility to carcinogens whether transplanted to young or old recipients (149). Do changes in cells in culture parallel changes in cells from aging organisms? The replicative lifespan of fibroblasts in culture is inversely related to the maximum lifespan of several diverse vertebrate species (150). Studies suggest that the replicative lifespan of cells in culture is inversely related to the age of the donor in both humans and rodents (151 – 153). This *in vivo-in vitro* relationship also holds for several different cell types, including hepatocytes (154), keratinocytes (155), and arterial smooth muscle cells (144). However, in these cross-sectional studies, there is a great deal of variability, and the correlation coefficient, though statistically significant, is low. Cells cultured from healthy individuals do not appear to exhibit a consistent age-related proliferative capacity (156). Cells from people with Werner's syndrome do senesce more rapidly in culture than age-matched controls; however, a consistently similar relationship does not hold for cells from people with Hutchinson-Gilford syndrome (121). Thus, under some circumstances, the proliferative characteristics of cells during aging *in vivo* are maintained in culture. Unfortunately, convincing evidence that senescent cells accumulate with age *in vivo* is lacking to date. A potential biomarker for aging, ß-galactosidase, has been described; it initially seemed to distinguish between senescent cells and either pre-senescent or quiescent cells (157). However, subsequent data indicate that *in situ* expression of ß-galactosidase exists in confluent, quiescent, pre-senescent cells and is not necessarily specific for senescence (e.g., possibly lysosomal damage rather than senescence *per se*) (158). Rubin proposes that the *in vitro* limit on replication is an artifact that reflects the cells' traumatic response to establishment *in vitro* and that their subsequent maintenance in a foreign environment is starkly different from their *in vivo* milieu (159). He suggests that a decline in the rate of cellular proliferation more accurately correlates with aging in animals.

A major approach to studying the regulation of cessation of replication in senescent cells has been to examine pathways, at various levels, which likely play significant roles in regulating cell proliferation and adaptive responses. Senescent cells are often less responsive to mitogens but can exhibit variable changes in growth-factor and growth-factor receptor expression compared to young cells (160). Senescent-related alterations in signal transduction pathways and nuclear transcription factors have also been documented. These alterations indicate that senescent cells exist in a growth state that is quite distinct from that of young cells and hint at the complex alteration in cellular physiology during senescence.

The phenomenon of telomere shortening with aging represents a potential "clock" or counting mechanism for senescent cells (161). Telomeres are structures at the end of chromosomes that prevent degradation and fusion with other chromosome ends (162). The average length of the terminal restriction fragment of chromosomes decreases with both *in vitro* and *in vivo* aging of fibroblasts and peripheral blood lymphocytes (161, 163 – 167). Indeed, telomere length in lymphocytes progressively declines as a function of donor age from newborn to great-grandparents in their eighties (168). Immortalized and transformed cells and germline cells express telomerase, which prevents shortening of the telomeres (169, 170). However, some immortal cells exist without detectable telomerase (171), and stem cells and some normal somatic cells which express telomerase, continue to experience telomeric shortening (172 – 174). These data suggest that the length of the telomeres *per se*, rather than the degree of telomerase activity, is the more important factor in cellular senescence. A recent study further demonstrates that the shortest telomere, not the average telomere length, determines cell viability and chromosomal stability (175). Experimental nonenzymatic elongation of telomeres extends the lifespan of cells (176). Furthermore, reactivation of telomerase, via the introduction of the telomerase reverse transcriptase unit into normal human cells, increases telomere length and extends the lifespan of both retinal epithelial cells and foreskin fibroblasts (177). Cells that had exceeded their normal lifespan by 20 population doublings exhibited normal karyotype and morphology similar to their younger counterparts. Shortened telomeres also led to a form of premature aging *in vivo* (178). Sixth generation telomerase-deficient mice with markedly shortened telomeres exhibited decreased weight and fecundity, graying and alopecia, increased ulcers and cancer, and shortened lifespan.

Products of the retinoblastoma (Rb) and p53 tumor-suppressor genes have also been implicated in replicative senescence (179, 180). Although similar levels of p53 are expressed in young and old cells *in vitro*, both DNA binding and transcriptional activity are increased in senescent cells (181). The Rb gene product is not phosphorylated in senescent cells (182). Simian virus 40 large T antigen, which is bound by the p53 and Rb gene products, can facilitate escape from senescence (183). T-antigen deletion mutants that lack either Rb- or p53-binding domains are unable to mediate escape from senescence (184). Furthermore, treatment with antisense oligonucleotides to the Rb and p53 tumor-suppressor genes can extend the *in vitro* lifespan of human fibroblasts (185). The p21 (186–188) and p16 (189–191) inhibitors of cyclin kinases (and therefore cell cycle progression) are overexpressed in senescent cells. The p21 protein appears to act by forming complexes with members of the family of E2F transcription factors in senescent cells (Rb/CDK2 [cyclin-dependent kinase 2]/cyclin E or with the Rb-related p107/CDK2/cyclin D), downregulating transcriptional activity and thereby inhibiting progression through the cell cycle (186). Targeted disruption of the p21 gene delays the onset of senescence in fibroblasts derived from human lung (192). However, adrenocortical cells express high levels of p21 throughout their *in vitro* lifespan up to and including senescence (193). Skin fibroblasts from patients with Li-Fraumeni syndrome are heterozygous for p53. In culture, these cells lose the remaining p53 allele and are subsequently unable to express p21, but still undergo *in vitro* aging (194), suggesting that p53 and p21 are not required for senescence. In senescent cells, p16 complexes to and inhibits both the cyclin-dependent kinase 4 (CDK4) and CDK6 cell cycle kinases (189). The *ras* oncogene product can induce senescence that is accompanied by accumulation of p53 and p16 (195). This occurs only in nonimmortalized cells and may reflect a homeostatic response of the cell to a transforming stimulus. Induction of expression of p16 by demethylation-dependent pathways or of p21 by demethylation-independent pathways can induce senescence in immortal fibroblasts that do not express p53 (196). Of those genes whose expression is required for G1/S cell cycle progression, senescent fibroblasts express no CDK2 and cyclin A, and reduced amounts of the G1 cyclins, C, D1, and E, compared to young cells (197). The expression of early G1 markers, but not late G1 markers, indicates that senescent cells may be blocked at a point in late G1.

The p53 gene plays an important role in a slew of critical cellular processes in addition to senescence, including cell cycle control, apoptosis, DNA repair, and transcription (198). Cells from telomerase-deficient mice (see above) exhibited high levels of p53 (199). In addition, deletion of p53 in the mice initially mitigated the effects of the telomerase deficiency, but ultimately contributed to greater malignant transformation. The p53 and p21 stress response is diminished in the p66shc null mice (also see above) that exhibit an increased lifespan (200). p53 has also been implicated in the effects exerted upon aging by radiation, oxidative stress, and the SIR2 gene (201). Recently p53 has been thrust to center stage in helping to increase our knowledge of the underlying mechanism(s) responsible for *in vivo* aging. Since p53-deficient mice die early due to marked increases in tumors, they do not represent a practical model to study aging. Therefore, Tyner et al. capitalized upon the serendipitous generation of a mouse that expresses a mutant p53 that enhances wild-type p53 activity (202). Not surprisingly, the mice are resistant to tumor development. However, the unexpected and fascinating finding is that the mice with augmented p53 activity also age prematurely and exhibit osteoporosis, generalized organ atrophy, diminished wound healing as well as stress tolerance, lymphoid atrophy, and reduced body weight. Consequently, it appears that increasing p53 activity reduces the incidence of cancer, but concurrently increases the aging rate (Fig. 5). A fine equilibrium between the antineoplastic and pro-aging characteristics of p53 may lead to the optimal lifespan for an organism; too little p53 results in death from can-

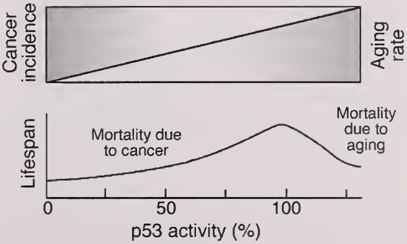

Fig. 5. Balancing cancer and aging. Adapted with permission from: Ferbeyre G, Lowe SW. The price of tumour suppression? Nature 2002; 415:26–27 (reference 201).

cer, whereas too much p53 leads to death by accelerated aging. Since p21 can be induced by p53-dependent mechanisms, it is possible that p21 is partly responsible for some of the observed aging phenotypes in these mice (203).

These observations emphasize the presence of complex and incompletely understood, overlapping networks regulating cell cycle progression and proliferation. Depending upon the balance of positive and negative influences, cell proliferation can continue or senescence may ensue. These data are consistent with the theory that cellular senescence evolved as a mechanism of tumor suppression and that aging is an antagonistically pleiotropic manifestation of evolutionary pressures to prevent malignant transformation, perhaps in large part via the actions of p53. The unavoidable conclusion is that cellular senescence is good for the organism; aging may be the price we pay to avoid, for the most part, cancer. However, even this concept has been qualified by the demonstration that senescent cells can foster the growth of premalignant and malignant epithelial cells in culture and the tumorigenesis of these cells in mice (204). The stimulation was due to both soluble and insoluble factors secreted by senescent cells. While these findings seem at odds with the beneficial effects of cellular senescence, they are themselves another example of antagonistic pleiotropy wherein a process that has evolved to protect against cancer may in fact predispose to cancer later in life.

Cell Death

There are two distinct patterns of cell death: necrosis and apoptosis. Massive cell injury, often accompanied by inflammation, can lead to necrosis. Necrosis is essentially accidental and entails clumping of chromatin into ill-defined masses, swelling of organelles, and ultimately membrane and cell disintegration (205). In contrast, apoptosis is an active, gene-directed "suicide" in response to external or internal stimuli, usually in the absence of significant external injury (205). In most circumstances, apoptosis is important, thereby permitting the organism to maintain homeostasis. Apoptosis initially involves compaction and segregation of chromatin adjacent to the nuclear membrane and condensation of the cytoplasm. This rapidly progresses to nuclear/cellular pedunculation and fragmentation. The membrane-bound apoptotic bodies are then phagocytosed by adjacent cells. Although "programmed cell death" and "apoptosis" are often used interchangeably, they are not actually synonymous terms. Lockshin and Zakeri (203) stress that programmed cell death is a developmental event, whereas apoptosis is a mode of cell death. Programmed cell death often involves increases of lysosomal enzyme and rarely exhibits the laddering of DNA seen in apoptosis. It is likely that programmed cell death is a type of apoptotic (controlled) cell death. Understanding the genetic basis of apoptosis initially depended upon work conducted in the nematode *C. elegans*, which has been a useful model system because the developmental fate of every cell has been determined (206); of the 1,090 cells formed, 131 eventually die. Three genes (*ced-3, ced-4,* and *ced-9*) play an important role in cell death in the nematode (207, 208). *Ced-3* is required for apoptosis in *C. elegans*; mammalian homologs include cysteine proteinases (ICE, CPP32, and ICH-1) (209). *Ced-9* blocks apoptosis; mammalian homologs include bcl-2 and bcl-X_L (208). Bcl-2 was originally identified as an oncogene because of its overexpression in a form of B-cell lymphoma. Additional mammalian homologs of bcl-2, which promote apoptosis, include bax, bad, and bak (210). Bcl gene family members can form homodimers or heterodimers, permitting a fine degree of control of cell survival. Heterodimerization with either bcl-2 or bcl-X_L prevents cell death.

Research is ongoing to elucidate the possible role of apoptosis in aging and diseases associated with aging. If cells are unable to repair DNA damage, apoptosis may ensue, followed by replacement via division of another cell. Senescent fibroblasts in culture are resistant to apoptotic signals, being unable to downregulate bcl-2 expression (211). This raises the possibility that damaged senescent cells may accumulate with increased organismal age, potentially compromising tissue function. Induction of apoptosis in the livers of old rats by a genotoxic agent is significantly reduced, compared to the induction of apoptosis in the livers of young rats (212). Caloric restriction in rodents upregulates apoptosis in the liver via the removal of preneoplastic cells (213, 214). Warner et al. suggest that this may counteract the diminished apoptosis in aging and explain life extension induced by caloric restriction (215). Apoptosis plays a critical role in the immune system, where as many as 95% of T lymphocytes undergo cell death (presumably because they recognize self-antigens) (216). Lymphocyte apoptosis is mediated by a cell-surface receptor, Fas. Mice lacking Fas exhibit increased autoimmune disease and are short lived. Caloric restriction in such mice increases T-lymphocyte apoptosis and extends lifespan (217). Fas expression decreases in older mice, and transgenic overexpression maintains Fas-induced apoptosis (218). Cell death is a characteristic in a number of neurodegenerative diseases common in aging (219). Specific neuronal loss is seen in Alzheimer's disease (hippocampus and cortex), Parkinson's disease (substantia nigra), Huntington's disease (striatum), and amyotrophic lateral sclerosis (motor neurons). β-amyloid protein is cytotoxic to cultured neuronal cells, which then undergo apoptosis.

Conclusions

Despite the near-universal phenomenon of aging in living organisms, there is an extraordinarily varied phenotype that accompanies aging in specific individuals. Furthermore, it appears that evolutionary pressures have led to the development of a remarkable homeostatic complexity to the underlying mechanisms that cause us to grow old. The three quotations at the beginning of this article aptly represent these processes. Butch Cassidy recognized the inexorable forces that cause us to age. The concept of antagonistic pleiotropy is reflected in the other two insights. It seems that we clearly pay a price to maintain a high level of reproductive fitness — there is no free lunch. However, the ironic, yet ultimately satisfying, paradox may be that the only way that we can actually live as long as we do is, in fact, to grow old.

References

1. Butch Cassidy and the Sundance Kid. Http://www.filmsite.org/butc.html; Review by Tom Dirks.
2. Anonymous. In: The Columbia world of quotations. New York: Columbia University Press; 1996.
3. Daniel Francois Esprit Auber. In: Bloomsbury biographic dictionary of quotations. London (UK): Bloomsbury; 1997; Http://www.bloomsburymagazine.com
4. Cutler RG. Evolutionary perspective of human longevity. In: Hazzard WR, Andres R, Bierman EL, Blass JP, editors. Principles of geriatric medicine and gerontology. New York: McGraw-Hill, 1990. pp. 15–21.
5. Monthly Vital Statistics Report. Hyattsville (MD): National Center for Health Statistics; 1997 June 12. No. 11(S)2. Vol. 45.
6. Sixty-five plus in the United States. Bureau of the Census Statistical Brief, U.S. Department of Commerce. May 1995. SB/95-8.
7. Roush W. Live long and prosper? [news]. Science 1996; 273:42–46.
8. Greville TN, Bayo F, Foster R. United States life tables by causes of death: 1960–1971. Hyattsville (MD): Technical Report — DHEW Publication. 1975 May. Publication #75/1150-Vol-1-5.
9. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. Science 1996; 273:59–63.
10. Weindruch R, Walford RL. Dietary restriction in mice beginning at 1 year of age: effect on life-span and spontaneous cancer incidence. Science 1982; 215:1415–1418.
11. Yu BP, Masoro EJ, McMahan CA. Nutritional influences on aging of Fischer 344 rats: 1. Physical, metabolic, and longevity characteristics. J Gerontol 1985; 40:657–670.
12. Masoro EJ. Dietary restriction and aging. J Am Geriatr Soc 1993; 41:994–999.
13. Weindruch R, Sohal RS. Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. N Engl J Med 1997; 337:986–994.
14. Dulloo AG, Girardier L. 24 hour energy expenditure several months after weight loss in the underfed rat: evidence for a chronic increase in whole-body metabolic efficiency. Int J Obes Relat Metab Disord 1993; 17:115–123.
15. Gonzales-Pacheco DM, Buss WC, Koehler KM, et al. Energy restriction reduces metabolic rate in adult male Fisher-344 rats. J Nutr 1993; 123:90–97.
16. McCarter R, Masoro EJ, Yu BP. Does food restriction retard aging by reducing the metabolic rate? Am J Physiol 1985; 248:E488–E490.
17. Lane MA, Baer DJ, Rumpler WV, et al. Calorie restriction lowers body temperature in rhesus monkeys, consistent with a postulated anti-aging mechanism in rodents. Proc Natl Acad Sci U S A 1996; 93:4159–4164.
18. Ramsey JJ, Roecker EB, Weindruch R, Kemnitz JW. Energy expenditure of adult male rhesus monkeys during the first 30 mo of dietary restriction. Am J Physiol 1997; 272(5 Pt 1):E901–E907.
19. Verdery RB, Ingram DK, Roth GS, Lane MA. Caloric restriction increases HDL2 levels in rhesus monkeys (Macaca mulatta). Am J Physiol 1997; 273:E714–E719.
20. Lane MA, Ingram DK, Ball SS, Roth GS. Dehydroepiandrosterone sulfate: a biomarker of primate aging slowed by calorie restriction. J Clin Endocrinol Metab 1997; 82: 2093–2096.
21. Gompertz B. On the nature of the function expressive of the law of human mortality and on a new mode of determining life contingencies. Philos Trans R Soc Lond 1825; 115: 513–585.
22. Rosenberg HM, Ventura SJ, Maurer JD, et al. Births and deaths: United States, 1995. Monthly Vital Statistics Report 1996; 45:31–33.
23. Kaeberlein M, McVey M, Guarente L. Using yeast to discover the fountain of youth. In: Science of aging and knowledge environment. Washington (DC): American Association for the Advancement of Science; New Findings Perspectives; 2001; http://sageke.sciencemag.org/cgi/content/full/sageke;2001/1/pe1
24. Shock NW, Greulich RC, Andres R, et al. Normal human aging: the Baltimore longitudinal study of aging. Washington (DC): Department of Health and Human Services (US); 1984. NIH Publication No. 84-2450.
25. Riggs BL, Melton LD. Involutional osteoporosis. N Engl J Med 1986; 314:16761–1686.
26. Florini JR, editor. Composition and function of cells and tissues. Handbook of biochemistry in aging. Boca Raton (FL): CRC Press; 1981.
27. Strehler BL. Time, cells, and aging. New York: Academic Press; 1977.
28. Bjorksten J. Cross linkage and the aging process. In: Rothstein M, editor. Theoretical aspects of aging. New York: Academic Press; 1974. pp. 43–60.
29. Kohn RR. Aging of animals: possible mechanisms. In: Kohn RR, editor. Principles of mammalian aging. Englewood Cliffs (NJ): Prentice-Hall; 1978.

30. Finch CE. Introduction: definitions and concepts. In: Finch CE. Longevity, senescence, and the genome. Chicago: University of Chicago Press; 1990.
31. Schneider EL, Rowe JW, editors. Handbook of the biology of aging. San Diego (CA): Academic Press; 1996.
32. Shock NW. Longitudinal studies of aging in humans. In: Finch CE, Schneider EL, editors. Handbook of the biology of aging. New York: Van Nostrand Reinhold; 1985. p. 721.
33. Lakatta EG. Changes in cardiovascular function with aging. Eur Heart J 1990; (11 Suppl C):22–29.
34. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc 1985; 33:278–285.
35. Adelman RC, Britton GW, Rotenberg S, et al. Endocrine regulation of gene activity in aging animals of different genotypes. In: Bergsma D, Harrison DE, editors. Genetic effects on aging. New York: Alan R. Liss; 1978. p. 355.
36. Brody JA, Brock DB. Epidemiological and statistical characteristics of the United States elderly population. In: Finch CE, Schneider EL, editors. Handbook of the biology of aging. New York: Van Nostrand Reinhold; 1985. p. 3.
37. Hitt R, Young-Xu Y, Silver M, Perls T. Centenarians: the older you get, the healthier you have been. Lancet 1999; 354:652.
38. Rose MR, Graves JL, Jr. What evolutionary biology can do for gerontology. J Gerontol 1989; 44:B27–B29.
39. Kirkwood TB, Rose MR. Evolution of senescence: late survival sacrificed for reproduction. Philos Trans R Soc Lond B Biol Sci 1991; 332:15–24.
40. Kirkwood TB. Human senescence. Bioessays 1996; 18:1009–1016.
41. Failla G. The aging process and carcinogenesis. Ann N Y Acad Sci 1958: 71:1124–1140.
42. Szilard L. On the nature of the aging process. Proc Natl Acad Sci U S A 1959; 45:30–45.
43. Walburg HE. Radiation-induced life-shortening and premature aging. Advances in Radiation Biology 1975; 5:145–179.
44. Sacher CA. Life table modification and life prolongation. In: Finch CE, Hayflick L, editors. Handbook of the biology of aging. New York: Van Nostrand Reinhold; 1977. pp. 582–638.
45. Lindop PJ, Rotblat J. Life-shortening in mice exposed to radiation: effects of age and of hypoxia. Nature 1965; 208(15):1070–1072.
46. Hart RW, Setlow RB. Correlation between deoxyribonucleic acid excision-repair and life- span in a number of mammalian species. Proc Natl Acad Sci U S A 1974; 71: 2169–2173.
47 Hanawalt PC, Gee P, Ho L, et al. Genomic heterogeneity of DNA repair. Role in aging? Ann N Y Acad Sci 1992; 663: 17–25.
48. Orgel LE The maintenance of the accuracy of protein synthesis and its relevance to aging. Proc Natl Acad Sci U S A 1963; 49:517–521
49. Kristal BS, Yu BP An emerging hypothesis: synergistic induction of aging by free radicals and Maillard reactions. J Gerontol 1992; 47:B107–B114.
50 Levine RL, Stadtman ER. Protein modifications with aging. In: Schneider EL, Rowe JW, editors. Handbook of the biology of aging San Diego (CA): Academic Press; 1996. pp. 184–197.
51. Gracy RW, Yuksel KU, Chapman MD, et al. Impaired protein degradation may account for the accumulation of "abnormal" proteins in aging cells. In: Adelman RC, Dekker EE, editors Modern aging research, modification of proteins during aging New York Alan R. Liss; 1985. pp. 1–18.
52 Reiser KM, Hennessy SM, Last JA. Analysis of age-associated changes in collagen crosslinking in the skin and lung in monkeys and rats Biochim Biophys Acta 1987; 926: 339–348
53. Hall DA. Chemical and biochemical changes in aging connective tissues. The aging of connective tissue. New York: Academic Press; 1976.
54. Chavous DA, Jackson FR, O'Connor CM. Extension of the Drosophila lifespan by overexpression of a protein repair methyltransferase. Proc Natl Acad Sci U S A 2001; 98: 14814–14818.
55. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol 1956; 11:298–300.
56. Harman D. The aging process. Proc Natl Acad Sci U S A 1981; 78:7124–7128.
57. Fridovich I. Superoxide dismutases. An adaptation to a paramagnetic gas. J Biol Chem 1989; 264:7761–7764.
58. Sen CK, Packer L. Antioxidant and redox regulation of gene transcription [see comments]. FASEB J 1996; 10:709–720.
59. Suzuki YJ, Forman HJ, Sevanian A. Oxidants as stimulators of signal transduction. Free Radic Biol Med 1997; 22: 269–285.
60. Sohal RS, Svensson I, Sohal BH, Brunk UT. Superoxide anion radical production in different animal species. Mech Ageing Dev 1989; 49:129–135.
61. Orr WC, Sohal RS. Extension of life-span by overexpression of superoxide dismutase and catalase in Drosophila melanogaster. Science 1994; 263:1128–1130.
62. Linnane AW, Zhang C, Baumer A, Nagley P. Mitochondrial DNA mutation and the ageing process: bioenergy and pharmacological intervention. Mutat Res 1992; 275:195–208.
63. Fleming JE, Miquel J, Cottrell SF, et al. Is cell aging caused by respiration-dependent injury to the mitochondrial genome? Gerontology 1982; 28:44–53.
64. Wallace DC. Mitochondrial genetics: a paradigm for aging and degenerative diseases? Science 1992; 256:628–632.
65. Ozawa T. Genetic and functional changes in mitochondria associated with aging. Physiol Rev 1997; 77:425–464.
66. Katayama M, Tanaka M, Yamamoto H, et al. Deleted mitochondrial DNA in the skeletal muscle of aged individuals. Biochem Int 1991; 25:47–56.
67. Lee CM, Chung SS, Kaczkowski JM, et al. Multiple mitochondrial DNA deletions associated with age in skeletal muscle of rhesus monkeys. J Gerontol 1993; 48:B201–B215.
68. Melov S, Shoffner JM, Kaufman A, Wallace DC. Marked increase in the number and variety of mitochondrial DNA rearrangements in aging human skeletal muscle [published erratum appears in Nucleic Acids Res 1995 Dec 11;23(23):4938]. Nucleic Acids Res 1995; 23:4122–4126.
69. Torii K, Sugiyama S, Tanaka M, et al. Aging-associated deletions of human diaphragmatic mitochondrial DNA. Am J Respir Cell Mol Biol 1992; 6:543–549.
70. Hayakawa M, Torii K, Sugiyama S, et al. Age-associated accumulation of 8-hydroxydeoxyguanosine in mitochondrial DNA of human diaphragm. Biochem Biophys Res Commun 1991; 179:1023–1029.
71. Sugiyama S, Hattori K, Hayakawa M, Ozawa T. Quantitative analysis of age-associated accumulation of mitochondrial DNA with deletion in human hearts. Biochem Biophys Res Commun 1991; 180:894–899.
72. Hayakawa M, Katsumata K, Yoneda M, et al. Age-related extensive fragmentation of mitochondrial DNA into minicircles [published erratum appears in Biochem Biophys Res Commun 1997 Mar 27;232(3):832]. Biochem Biophys Res Commun 1996; 226:369–377.
73. Hayakawa M, Hattori K, Sugiyama S, Ozawa T. Age-associated oxygen damage and mutations in mitochondrial DNA in human hearts. Biochem Biophys Res Commun 1992; 189:979–985.
74. Hayakawa M, Sugiyama S, Hattori K, et al. Age-associated damage in mitochondrial DNA in human hearts. Mol Cell Biochem 1993; 119:95–103.

75. Ikebe S, Tanaka M, Ohno K, et al. Increase of deleted mitochondrial DNA in the striatum in Parkinson's disease and senescence. Biochem Biophys Res Commun 1990; 170: 1044–1048.
76. Corral-Debrinski M, Horton T, Lott MT, et al. Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age. Nat Genet 1992; 2:324–329.
77. Trounce I, Byrne E, Marzuki S. Decline in skeletal muscle mitochondrial respiratory chain function: possible factor in ageing [see comments]. Lancet 1989; 1:637–639.
78. Schapira AH, Mann VM, Cooper JM, et al. Anatomic and disease specificity of NADH CoQ1 reductase (complex I) deficiency in Parkinson's disease. J Neurochem 1990; 55: 2142–2145.
79. Schapira AH, Cooper JM, Dexter D, et al. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem 1990; 54:823–827.
80. Hoyer S. Senile dementia and Alzheimer's disease. Brain blood flow and metabolism. Prog Neuropsychopharmacol Biol Psychiatry 1986; 10:447–478.
81. Sims NR, Finegan JM, Blass JP, et al. Mitochondrial function in brain tissue in primary degenerative dementia. Brain Res 1987; 436:30–38.
82. Beal MF. Neurochemistry and toxin models in Huntington's disease. Curr Opin Neurol 1994; 7:542–547.
83. Schulz JB, Beal MF. Mitochondrial dysfunction in movement disorders. Mech Dev 1996; 57:3–20.
84. Lin FH, Lin R, Wisniewski HM, et al. Detection of point mutations in codon 331 of mitochondrial NADH dehydrogenase subunit 2 in Alzheimer's brains. Biochem Biophys Res Commun 1992; 182:238–246.
85. Shoffner JM, Brown MD, Torroni A, et al. Mitochondrial DNA variants observed in Alzheimer disease and Parkinson disease patients. Genomics 1993; 17:171–184.
86. Ozawa T, Tanaka M, Ino H, et al. Distinct clustering of point mutations in mitochondrial DNA among patients with mitochondrial encephalomyopathies and with Parkinson's disease. Biochem Biophys Res Commun 1991; 176:938–946.
87. Ozawa T, Tanaka M, Ikebe S, et al. Quantitative determination of deleted mitochondrial DNA relative to normal DNA in parkinsonian striatum by a kinetic PCR analysis. Biochem Biophys Res Commun 1990; 172:483–489.
88. Ikebe S, Tanaka M, Ozawa T. Point mutations of mitochondrial genome in Parkinson's disease. Brain Res Mol Brain Res 1995; 28:281–295.
89. Poulton J, Deadman ME, Ramacharan S, Gardiner RM. Germline deletions of mtDNA in mitochondrial myopathy. Am J Hum Genet 1991; 48:649–653.
90. Ionasescu VV, Hart M, DiMauro S, Moraes CT. Clinical and morphologic features of a myopathy associated with a point mutation in the mitochondrial tRNA(Pro) gene. Neurology 1994; 44:975–977.
91. Ozawa T, Tanaka M, Sugiyama S, et al. Patients with idiopathic cardiomyopathy belong to the same mitochondrial DNA gene family of Parkinson's disease and mitochondrial encephalomyopathy. Biochem Biophys Res Commun 1991; 177:518–525.
92. Katsumata K, Hayakawa M, Tanaka M, et al. Fragmentation of human heart mitochondrial DNA associated with premature aging. Biochem Biophys Res Commun 1994; 202:102–110.
93. Ozawa T. Mitochondrial cardiomyopathy. Herz 1994; 19: 105–125.
94. Yoneda M, Katsumata K, Hayakawa M, et al. Oxygen stress induces an apoptotic cell death associated with fragmentation of mitochondrial genome. Biochem Biophys Res Commun 1995; 209:723–729.
95. Melov S, Hinerfeld D, Esposito L, Wallace DC. Multi-organ characterization of mitochondrial genomic rearrangements in ad libitum and caloric restricted mice show striking somatic mitochondrial DNA rearrangements with age. Nucleic Acids Res 1997; 25:974–982.
96. De Benedictis G, Rose G, Carrieri G, et al. Mitochondrial DNA inherited variants are associated with successful aging and longevity in humans. FASEB J 1999; 13:1532–1536.
97. Rose G, Passarino G, Carrieri G, et al. Paradoxes in longevity: sequence analysis of mtDNA haplogroup J in centenarians. Eur J Hum Genet 2001; 9:701–707.
98. Ross OA, McCormack R, Curran MD, et al. Mitochondrial DNA polymorphism: its role in longevity of the Irish population. Exp Gerontol 2001; 36:1161–1178.
99. Larsen PL, Clarke CF. Extension of life-span in Caenorhabditis elegans by a diet lacking coenzyme Q. Science 2002; 295: 120–123.
100. Zainal TA, Oberley TD, Allison DB, et al. Caloric restriction of rhesus monkeys lowers oxidative damage in skeletal muscle. FASEB J 2000; 14:1825–1836.
101. Meydani M. Nutrition interventions in aging and age-associated disease. Ann N Y Acad Sci 2001; 928:226–235.
102. Finch CE, Tanzi RE. Genetics of aging. Science 1997; 278: 407–411.
103. Jazwinski SM. Longevity, genes, and aging. Science 1996; 273:54–59.
104. Murakami S, Johnson TE. A genetic pathway conferring life extension and resistance to UV stress in Caenorhabditis elegans. Genetics 1996; 143:1207–1218.
105. Kimura KD, Tissenbaum HA, Liu Y, Ruvkun G. daf-2, an insulin receptor-like gene that regulates longevity and diapause in Caenorhabditis elegans [see comments]. Science 1997; 277:942–946.
106. Kenyon C, Chang J, Gensch E, et al. A C. elegans mutant that lives twice as long as wild type [see comments]. Nature 1993; 366:461–464.
107. Lin K, Dorman JB, Rodan A, Kenyon C. daf-16: an HNF-3/forkhead family member that can function for double the life-span of Caenorhabditis elegans. Science 1997; 278: 1319–1322.
108. Lin YJ, Seroude L, Benzer S. Extended life-span and stress resistance in the Drosophila mutant Methuselah. Science 1998; 282:943–946.
109. Rogina B, Reenan RA, Nilsen SP, Helfand SL. Extended life-span conferred by cotransporter gene mutations in Drosophila. Science 2000; 290:2137–2140.
110. Dudas SP, Arking R. A coordinate upregulation of antioxidant gene activities is associated with the delayed onset of senescence in a long-lived strain of Drosophila. J Gerontol A Biol Sci Med Sci 1995; 50:B117–B127.
111. Rose MR, Vu LN, Park SU, Graves JL, Jr. Selection on stress resistance increases longevity in Drosophila melanogaster. Exp Gerontol 1992; 27:241–250.
112. Lithgow GJ, Andersen JK. The real Dorian Gray mouse. Bioessays 2000; 22:410–413.
113. Flurkey K, Papaconstantinou J, Harrison DE. The Snell dwarf mutation Pit1(dw) can increase life span in mice. Mech Ageing Dev 2002; 123:121–130.
114. Schachter F, Faure-Delanef L, Guenot F, et al. Genetic associations with human longevity at the APOE and ACE loci. Nat Genet 1994; 6:29–32.
115. Perls T, Levenson R, Regan M, Puca A. What does it take to live to 100? Mech Ageing Dev 2002; 123:231–242.
116. Lee CK, Klopp RG, Weindruch R, Prolla TA. Gene expression profile of aging and its retardation by caloric restriction. Science 1999; 285:1390–1393.

117. Lee CK, Weindruch R, Prolla TA. Gene-expression profile of the ageing brain in mice. Nat Genet 2000; 25:294–297.
118. Kayo T, Allison DB, Weindruch R, Prolla TA. Influences of aging and caloric restriction on the transcriptional profile of skeletal muscle from rhesus monkeys. Proc Natl Acad Sci U S A 2001; 98:5093–5098.
119. Weindruch R, Kayo T, Lee CK, Prolla TA. Microarray profiling of gene expression in aging and its alteration by caloric restriction in mice. J Nutr 2001; 131:918S–923S.
120. Turker MS, Martin GM. Genetics of human disease, longevity and aging. In: Hazzard WR, Blass JP, Ettinger WH, Jr, Halter JB, editors. Principles of geriatric medicine and gerontology. 4th ed. London: McGraw-Hill; 1999. pp. 21–44.
121. Brown WT. Genetic diseases of premature aging as models of senescence. Annu Rev Gerontol Geriatr 1990; 10:23–42.
122. Goto M, Rubenstein M, Weber J, et al. Genetic linkage of Werner's syndrome to five markers on chromosome 8. Nature 1992; 355:735–738.
123. Yu CE, Oshima J, Fu YH, et al. Positional cloning of the Werner's syndrome gene [see comments]. Science 1996; 272:258–262.
124. Kuro-o M. Disease model: human aging. Trends Mol Med 2001; 7:179–181.
125. Mobbs CV. Neuroendocrinology of aging. In: Schneider EL, Rowe JW, editors. Handbook of the biology of aging. San Diego (CA): Academic Press, 1996. pp. 234–282.
126. Wise PM, Krajnak KM, Kashon ML. Menopause: the aging of multiple pacemakers. Science 1996; 273:67–70.
127. Denckla WD. A time to die. Life Sci 1975; 16:31–44.
128. Gilad GM, Gilad VH. Age-related reductions in brain cholinergic and dopaminergic indices in two rat strains differing in longevity. Brain Res 1987; 408:247–250.
129. Cotzias GC, Miller ST, Tang LC, Papavasiliou PS. Levodopa, fertility, and longevity. Science 1977; 196:549–551.
130. Knoll J. (-)Deprenyl-medication: a strategy to modulate the age-related decline of the striatal dopaminergic system. J Am Geriatr Soc 1992; 40:839–847.
131. Kitani K, Kanai S, Sato Y, et al. Chronic treatment of (-) deprenyl prolongs the life span of male Fischer 344 rats. Further evidence. Life Sci 1993; 52:281–288.
132. Milgram NW, Racine RJ, Nellis P, et al. Maintenance on L-deprenyl prolongs life in aged male rats. Life Sci 1990; 47: 415–420.
133. Walford RL. Immunologic theory of aging: current status. Fed Proc 1974; 33:2020–2027.
134. Miller RA. The aging immune system: primer and prospectus. Science 1996; 273:70–74.
135. Yunis EJ, Salazar M. Genetics of life span in mice. Genetica 1993; 91:211–223.
136. Caruso C, Candore G, Romano GC, et al. Immunogenetics of longevity. Is major histocompatibility complex polymorphism relevant to the control of human longevity? A review of literature data. Mech Ageing Dev 2001; 122: 445–462.
137. Hayflick L, Moorhead PS. The limited in vitro lifetime of human diploid cell strains. Exp Cell Res 1965; 37:614–636.
138. Bayreuther K, Rodemann HP, Hommel R, et al. Human skin fibroblasts in vitro differentiate along a terminal cell lineage. Proc Natl Acad Sci U S A 1988; 85:5112–5116.
139. Pignolo RJ, Rotenberg MO, Cristofalo VJ. Alterations in contact and density-dependent arrest state in senescent WI-38 cells. In Vitro Cell Dev Biol Anim 1994; 30A:471–476.
140. Matsumura T, Zerrudo Z, Hayflick L. Senescent human diploid cells in culture: survival, DNA synthesis and morphology. J Gerontol 1979; 34:328–334.
141. Cristofalo VJ, Palaxxo R, Charpentier RL. Limited lifespan of human fibroblasts in vitro: metabolic time or replications? In: Adelman RC, Roberts J, Baker GT, et al., editors. Neural regulatory mechanisms during aging. New York: Alan R. Liss; 1980. pp. 203–206.
142. Ponten J, Stein WD, Shall S. A quantitative analysis of the aging of human glial cells in culture. J Cell Physiol 1983; 117(3):342–352.
143. Rheinwald JG, Green H. Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. Cell 1975; 6:331–343.
144. Bierman EL. The effect of donor age on the in vitro life span of cultured human arterial smooth-muscle cells. In Vitro 1978; 14:951–955.
145. Tassin J, Malaise E, Courtois Y. Human lens cells have an in vitro proliferative capacity inversely proportional to the donor age. Exp Cell Res 1979; 123:388–392.
146. Mueller SN, Rosen EM, Levine EM. Cellular senescence in a cloned strain of bovine fetal aortic endothelial cells. Science 1980; 207:889–891.
147. Tice RR, Schneider EL, Kram D, Thorne P. Cytokinetic analysis of the impaired proliferative response of peripheral lymphocytes from aged humans to phytohemagglutinin. J Exp Med 1979; 149:1029–1041.
148. Harrison DE. Cell and tissue transplantation: a means of studying the aging process. In: Finch CE, Schneider EL, editors. Handbook of the biology of aging. New York: Van Nostrand Reinhold; 1985. p. 332–356.
149. Olsson L, Ebbesen P. Ageing decreases the activity of epidermal G1 and G2 inhibitors in mouse skin independent of grafting on old or young recipients. Exp Gerontol 1977; 12: 59–62.
150. Rohme D. Evidence for a relationship between longevity of mammalian species and life spans of normal fibroblasts in vitro and erythrocytes in vivo. Proc Natl Acad Sci U S A 1981; 78:5009–5013.
151. Martin GM, Sprague CA, Epstein CJ. Replicative life-span of cultivated human cells. Effects of donor's age, tissue, and genotype. Lab Invest 1970; 23:86–92.
152. Pignolo RJ, Masoro EJ, Nichols WW, et al. Skin fibroblasts from aged Fischer 344 rats undergo similar changes in replicative life span but not immortalization with caloric restriction of donors. Exp Cell Res 1992; 201:16–22.
153. Schneider EL, Mitsui Y. The relationship between in vitro cellular aging and in vivo human age. Proc Natl Acad Sci U S A 1976; 73:3584–3588.
154. Le Guilly Y, Simon M, Lenoir P, Bourel M. Long-term culture of human adult liver cells: morphological changes related to in vitro senescence and effect of donor's age on growth potential. Gerontologia 1973; 19:303–313.
155. Wille JJ, Jr., Pittelkow MR, Shipley GD, Scott RE. Integrated control of growth and differentiation of normal human prokeratinocytes cultured in serum-free medium: clonal analyses, growth kinetics, and cell cycle studies. J Cell Physiol 1984; 121:31–44.
156. Cristofalo VJ, Allen RG, Pignolo RJ, et al. Relationship between donor age and the replicative life span of human cells in culture: a reevaluation. Proc Natl Acad Sci U S A 1998; 95:10614–10619.
157. Dimri GP, Lee X, Basile G, et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc Natl Acad Sci U S A 1995; 92:9363–9367.
158. Severino J, Allen RG, Balin S, et al. Is beta-galactosidase staining a marker of senescence in vitro and in vivo? Exp Cell Res 2000; 257:162–171.

159. Rubin H. Cell aging in vivo and in vitro. Mech Ageing Dev 1997; 98:1–35.

160. Troen BR, Cristofalo VJ. Cell and molecular aging. In: Rosenthal RA, Zenilman ME, Katlic MR, editors. Principles and practice of geriatric surgery. New York: Springer; 2001. pp. 8–23.

161. Harley CB. Telomere loss: mitotic clock or genetic time bomb? Mutat Res 1991; 256:271–282.

162. Greider CW. Telomeres, telomerase and senescence. Bioessays 1990; 12:363–369.

163. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. Nature 1990; 345:458–460.

164. Allsopp RC, Vaziri H, Patterson C, et al. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci U S A 1992; 89:10114–10118.

165. Chang E, Harley CB. Telomere length and replicative aging in human vascular tissues. Proc Natl Acad Sci U S A 1995; 92: 11190–11194.

166. Lindsey J, McGill NI, Lindsey LA, et al. In vivo loss of telomeric repeats with age in humans. Mutat Res 1991; 256: 45–48.

167. Vaziri H, Schachter F, Uchida I, et al. Loss of telomeric DNA during aging of normal and trisomy 21 human lymphocytes. Am J Hum Genet 1993; 52:661–667.

168. Frenck RW, Jr., Blackburn EH, Shannon KM. The rate of telomere sequence loss in human leukocytes varies with age. Proc Natl Acad Sci U S A 1998; 95:5607–5610.

169. Counter CM, Hirte HW, Bacchetti S, Harley CB. Telomerase activity in human ovarian carcinoma [see comments]. Proc Natl Acad Sci U S A 1994; 91:2900–2904.

170. Sugihara S, Mihara K, Marunouchi T, et al. Telomere elongation observed in immortalized human fibroblasts by treatment with 60Co gamma rays or 4-nitroquinoline 1-oxide. Hum Genet 1996; 97:1–6.

171. Bryan TM, Englezou A, Gupta J, et al. Telomere elongation in immortal human cells without detectable telomerase activity. EMBO J 1995; 14:4240–4248.

172. Chiu CP, Dragowska W, Kim NW, et al. Differential expression of telomerase activity in hematopoietic progenitors from adult human bone marrow. Stem Cells 1996; 14:239–248.

173. Broccoli D, Young JW, de Lange T. Telomerase activity in normal and malignant hematopoietic cells. Proc Natl Acad Sci U S A 1995; 92:9082–9086.

174. Counter CM, Gupta J, Harley CB, et al. Telomerase activity in normal leukocytes and in hematologic malignancies. Blood 1995; 85:2315–2320.

175. Hemann MT, Strong MA, Hao LY, Greider CW. The shortest telomere, not average telomere length, is critical for cell viability and chromosome stability. Cell 2001; 107:67–77.

176. Wright WE, Brasiskyte D, Piatyszek MA, Shay JW. Experimental elongation of telomeres extends the lifespan of immortal x normal cell hybrids. EMBO J 1996; 15: 1734–1741.

177. Bodnar AG, Ouellette M, Frolkis M, et al. Extension of lifespan by introduction of telomerase into normal human cells [see comments]. Science 1998; 279:349–352.

178. Rudolph KL, Chang S, Lee HW, et al. Longevity, stress response, and cancer in aging telomerase-deficient mice. Cell 1999; 96:701–712.

179. Campisi J. Aging and cancer: the double-edged sword of replicative senescence. J Am Geriatr Soc 1997; 45:482–488.

180. Shay JW, Wright WE, Werbin H. Toward a molecular understanding of human breast cancer: a hypothesis. Breast Cancer Res Treat 1993; 25:83–94.

181. Atadja P, Wong H, Garkavtsev I, et al. Increased activity of p53 in senescing fibroblasts. Proc Natl Acad Sci U S A 1995; 92: 8348–8352.

182. Stein GH, Beeson M, Gordon L. Failure to phosphorylate the retinoblastoma gene product in senescent human fibroblasts. Science 1990; 249:666–699.

183. Ozer HL, Banga SS, Dasgupta T, et al. SV40-mediated immortalization of human fibroblasts. Exp Gerontol 1996; 31: 303–310.

184. Shay JW, Pereira-Smith OM, Wright WE. A role for both RB and p53 in the regulation of human cellular senescence. Exp Cell Res 1991; 196:33–39.

185. Hara E, Tsurui H, Shinozaki A, et al. Cooperative effect of antisense-Rb and antisense-p53 oligomers on the extension of life span in human diploid fibroblasts, TIG-1. Biochem Biophys Res Commun 1991; 179:528–534.

186. Afshari CA, Nichols MA, Xiong Y, Mudryj M. A role for a p21-E2F interaction during senescence arrest of normal human fibroblasts. Cell Growth Differ 1996; 7:979–988.

187. Noda A, Ning Y, Venable SF, et al. Cloning of senescent cell-derived inhibitors of DNA synthesis using an expression screen. Exp Cell Res 1994; 211:90–98.

188. Tahara H, Sato E, Noda A, Ide T. Increase in expression level of p21sdi1/cip1/waf1 with increasing division age in both normal and SV40-transformed human fibroblasts. Oncogene 1995; 10:835–840.

189. Alcorta DA, Xiong Y, Phelps D, et al. Involvement of the cyclin-dependent kinase inhibitor p16 (INK4a) in replicative senescence of normal human fibroblasts. Proc Natl Acad Sci U S A 1996; 93:13742–13747.

190. Palmero I, McConnell B, Parry D, et al. Accumulation of p16INK4a in mouse fibroblasts as a function of replicative senescence and not of retinoblastoma gene status. Oncogene 1997; 15:495–503.

191. Reznikoff CA, Yeager TR, Belair CD, et al. Elevated p16 at senescence and loss of p16 at immortalization in human papillomavirus 16 E6, but not E7, transformed human uroepithelial cells. Cancer Res 1996; 56:2886–2890.

192. Brown JP, Wei W, Sedivy JM. Bypass of senescence after disruption of p21CIP1/WAF1 gene in normal diploid human fibroblasts. Science 1997; 277:831–834.

193. Yang L, Didenko VV, Noda A, et al. Increased expression of p21Sdi1 in adrenocortical cells when they are placed in culture. Exp Cell Res 1995; 221:126–131.

194. Medcalf AS, Klein-Szanto AJ, Cristofalo VJ. Expression of p21 is not required for senescence of human fibroblasts. Cancer Res 1996; 56:4582–4585.

195. Serrano M, Lin AW, McCurrach ME, et al. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. Cell 1997; 88:593–602.

196. Vogt M, Haggblom C, Yeargin J, et al. Independent induction of senescence by p16INK4a and p21CIP1 in spontaneously immortalized human fibroblasts. Cell Growth Differ 1998; 9: 139–146.

197. Afshari CA, Vojta PJ, Annab LA, et al. Investigation of the role of G1/S cell cycle mediators in cellular senescence. Exp Cell Res 1993; 209:231–237.

198. Ryan KM, Phillips AC, Vousden KH. Regulation and function of the p53 tumor suppressor protein. Curr Opin Cell Biol 2001; 13:332–337.

199. Chin L, Artandi SE, Shen Q, et al. p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis. Cell 1999; 97: 527–538.

200. Migliaccio E, Giorgio M, Mele S, et al. The p66shc adaptor protein controls oxidative stress response and life span in mammals. Nature 1999; 402:309–313.

201. Ferbeyre G, Lowe SW. The price of tumour suppression? Nature 2002; 415:26–27.

202. Tyner SD, Venkatachalam S, Choi J, et al. p53 mutant mice that display early ageing-associated phenotypes. Nature 2002; 415:45–53.
203. Campisi J. Cancer and aging: Yin, yang, and p53. Science of aging and knowledge environment: American Association for the Advancement of Science and Science Magazine: 2002; http://sageke.sciencemag.org/cgi/content/full/sageke; 2001/1/pel
204. Krtolica A, Parrinello S, Lockett S, et al. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. Proc Natl Acad Sci U S A 2001; 98:12072–12077.
205. Lockshin RA, Zakeri Z. Programmed cell death and apoptosis. In: Tomei LD, Cope FO, editors. Apoptosis: the molecular basis of cell death. Plainview (NY): Cold Spring Harbor Laboratory Press; 1991. pp. 47–60.
206. Ellis RE, Yuan JY, Horvitz HR. Mechanisms and functions of cell death. Annu Rev Cell Dev Biol 1991; 7:663–698.
207. Yuan JY, Horvitz HR. The Caenorhabditis elegans genes ced-3 and ced-4 act cell autonomously to cause programmed cell death. Dev Biol 1990; 138:33–41.
208. Hengartner MO, Horvitz HR. C. elegans cell survival gene ced-9 encodes a functional homolog of the mammalian proto-oncogene bcl-2. Cell 1994; 76:665–676.
209. Nagata S. Apoptosis by death factor. Cell 1997; 88:355–365.
210. White E. Life, death, and the pursuit of apoptosis. Genes Dev 1996; 10:1–15.
211. Wang E. Senescent human fibroblasts resist programmed cell death, and failure to suppress bcl2 is involved. Cancer Res 1995; 55:2284–2292.
212. Suh Y, Lee KA, Kim WH, et al. Aging alters the apoptotic response to genotoxic stress. Nat Med 2002; 8:3–4.
213. Grasl-Kraupp B, Bursch W, Ruttkay-Nedecky B, et al. Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. Proc Natl Acad Sci U S A 1994; 91:9995–9999.
214. James SJ, Muskhelishvili L. Rates of apoptosis and proliferation vary with caloric intake and may influence incidence of spontaneous hepatoma in C57BL/6 x C3H F1 mice. Cancer Res 1994; 54:5508–5510.
215. Warner HR, Fernandes G, Wang E. A unifying hypothesis to explain the retardation of aging and tumorigenesis by caloric restriction. J Gerontol A Biol Sci Med Sci 1995; 50: B017–B109.
216. Jacobson MD, Weil M, Raff MC. Programmed cell death in animal development. Cell 1997; 88:347–354.
217. Luan X, Zhao W, Chandrasekar B, Fernandes G. Calorie restriction modulates lymphocyte subset phenotype and increases apoptosis in MRL/lpr mice. Immunol Lett 1995; 47:181–186.
218. Zhou T, Edwards CK, Mountz JD. Prevention of age-related T cell apoptosis defect in CD2-fas-transgenic mice [see comments]. J Exp Med 1995; 182:129–137.
219. Warner HR, Hodes RJ, Pocinki K. What does cell death have to do with aging? J Am Geriatr Soc 1997; 45:1140–1146.

Inflammatory Arthritis in the Elderly

LESLIE DUBIN KERR, M.D.

Abstract

The three most common inflammatory arthritic conditions affecting the elderly are reviewed, along with current information about the various treatments.

Key Words: Elderly, arthritis, rheumatoid arthritis, gout.

Introduction

ARTHRITIC COMPLAINTS in the elderly are most frequently associated with degenerative, noninflammatory osteoarthritis. Not uncommonly, however, forms of inflammatory arthritis, such as rheumatoid arthritis (RA), gout, or pseudogout, may be present. The ability to identify inflammatory arthritis is crucial, because these entities, unlike osteoarthritis, are highly responsive to pharmacologic intervention. With such intervention, the disabling symptoms associated with inflammatory arthritis can be markedly suppressed or eliminated, with improvement in the functional status and overall well-being of the elderly patient.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most prevalent inflammatory arthritis of any age group, occurring in 1–2% of the world's population, according to estimates by the Arthritis Foundation (1). The etiology and pathogenesis of RA are unknown. It is defined by clinical criteria, including significant generalized morning stiffness lasting for more than one hour; an objective symmetrical polyarthritis affecting three or more joints; a tendency for proximal hand joint involvement, e.g., in the wrist, metacarpophalangeal joints (MCPs), and proximal interphalangeal joints (PIPs); and the persistence of all symptoms for at least 6 weeks, in the absence of another defined connective tissue disease such as lupus, scleroderma, myositis, or vasculitis (2). Rheumatoid factor, rheumatoid nodules, and erosive changes on x-ray are not required for the diagnosis.

Rheumatoid arthritis is also quite common in the elderly, in whom two clinical presentations are encountered. The first, referred to as "RA in the elderly," is the *de novo* development of rheumatoid arthritis in persons older than age 65. Clinically, it is characterized by disabling morning stiffness and marked pain predominantly affecting the upper extremities. The physical examination is remarkable for pronounced synovitis of the shoulders and the wrists as well as the MCPs and PIPs, with marked limitation of motion and severe soft tissue swelling. These conditions result in striking functional impairment of the hands. Laboratory evaluation is remarkable only for an elevated sedimentation rate, and rheumatoid factor is frequently absent. X-rays reveal periarticular osteopenia and soft tissue swelling. Joint space narrowing and erosive changes are uncommon at initial presentation (3).

The second presentation of rheumatoid arthritis encountered in elderly patients affects

---

Address correspondence to Leslie Dubin Kerr, M.D., Associate Professor of Medicine and Geriatrics, Division of Rheumatology, Box 1244, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

This work is based on a presentation at the Geriatric Medicine Update and Board Review at the Mount Sinai School of Medicine, New York, NY on October 5–8, 2001.

those in whom the RA has developed before the age of 65. Most of these patients have had several decades of disease activity by the time they present to geriatricians. As a result, they commonly have an advanced stage of the disease, with multiple deformities in addition to prolonged morning stiffness. Often, they have already been treated with multiple agents which have failed to provide a remission or relief of symptoms. Not uncommonly, they have already undergone selective joint replacement surgery. The physical examination of these patients reveals varying degrees of active polyarticular synovitis in both the upper and lower extremities. Ulnar deviation, elbow contractures, wrist subluxation, swan-neck and Boutonniere deformities are also common. Systemic manifestations such as rheumatoid lung, vasculitic ulcers, peripheral neuropathy, and secondary amyloid, all reflecting longstanding inflammatory disease, may complicate the care of this subpopulation of RA patients.

In addition to an elevated sedimentation rate, many of these patients have elevated serum rheumatoid factor. X-rays reveal marked erosive, destructive joint disease in addition to prominent osteopenia and soft tissue swelling.

Therapeutic Approach to RA in the Elderly

For both groups of patients, those with *de novo* onset as well as those with longstanding disease, the primary therapeutic objectives are the relief of joint pain and improvement in functional status. These goals take on more urgency for the elderly, because the potential for immobility places them at high risk for permanent loss of their independence. Once these patients become bed- or chair-bound, medical complications such as decubitus ulcers and deep venous thrombosis make recovery improbable. For this reason, palliation with corticosteroids should begin immediately. Since the dosages required for suppression of rheumatoid synovitis in the geriatric patient are low, in the range of 2.5 – 7.5 mg per day, the long-term toxicity is minimal, as compared with younger rheumatoids. This contrasts with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the elderly rheumatoid, for whom suppression of inflammation is achieved only with high dosages of these drugs. The toxicity associated with the chronic use of these high dosages in the elderly is considerable, and results in gastrointestinal (GI) bleeding, GI perforation, renal failure, volume overload, and central nervous system (CNS) effects (5). The cyclo-oxygenase-2 (COX-2) inhibitors, although safer from the standpoint of adverse GI problems, cause impaired renal function, hypertension, altered fluid/electrolyte status, and CNS toxicity. Thus, high-dose chronic usage of NSAIDs for symptomatic control in the elderly rheumatoid is problematic, with the risk/benefit ratio for low-dose steroids markedly more attractive. For those elderly rheumatoids whose synovitis remains symptomatic despite several months of low-dose steroids, or who have either erosive, destructive arthritis or systemic extra-articular disease, treatment with remittive agents or disease-modifying antirheumatic drugs (DMARDs) is indicated (6).

The use of remittive agents in the elderly rheumatoid is the same as that in young rheumatoid patients and includes the use of broad-spectrum immunosuppressive drugs as well as newly developed biologic agents such as tumor necrosis factor (TNF) inhibitors and interleukin-1 receptor antagonists (see Table 1). Although preliminary data are promising, the long-term safety and efficacy of these new biologic agents has yet to be determined (7 – 9). In addition, the need for parenteral administration of these agents, coupled with the high frequency of contraindications found in this population, such as old TB, treated malignancy, or a chronic site of infection, limits their use in elderly rheumatoids.

For those elderly patients in whom drug therapy for rheumatoid arthritis is indicated, but who have significant underlying medical problems such as renal insufficiency, hepatic impairment, or myelodysplasia, or who cannot

TABLE 1

Remittive Therapy in Rheumatoid Arthritis

Immunosuppressive Agents
    aurothioglucose
    gold sodium thiomalate
    auranofin
    methotrexate
    hydroxychloroquine
    sulphasalazine
    cyclosporine
    azathioprine
    leflunomide
    mycophenolate mofetil
    cyclophosphamide
Biologic Agents
    etanercept*
    infliximab*
    anakinra*

* long-term data to establish efficacy not yet available

make frequent follow-up visits, hydroxychloroquine and low-dose sulphasalazine are less-toxic alternatives. These latter two drugs require less frequent monitoring for adverse effects (10). Physical therapy, supportive devices, and judicious joint replacement surgery are also of great benefit to elderly rheumatoids.

Gout

Gout is the second most commonly encountered inflammatory arthritis in the geriatric patient. It is caused by an intense inflammatory reaction to the shedding of monosodium urate crystals into synovial fluid (11). Alcohol use, renal insufficiency, diuretic use, dehydration, and acute medical illness are predisposing factors commonly seen in the elderly. The initial attack is usually monarticular, with the first metatarsophalangeal joint (MTP) as the most common site of inflammation. Subsequent attacks can be either monarticular or polyarticular, with intense pain, swelling, and erythema localized to the first MTPs, the dorsum of the foot, instep, ankle, knees, wrists, olecranon bursae, and distal digits. Gouty arthritis affecting the shoulder and spine is less commonly seen. Most acute attacks resolve spontaneously over 1–2 weeks if untreated. The severity of symptoms in those patients who experience a polyarticular attack makes gout disabling, particularly when they are unable to wear shoes, walk, or close their hands. For this reason, prompt diagnosis is important, especially since rapid and complete resolution of symptoms within a few days is probable with the appropriate treatment.

Gout is diagnosed by arthrocentesis, with the demonstration of intracellular uric acid crystals by polarized microscopy. The visualization of intracellular crystals rules out the possibility of a missed septic arthritis.

Treatment of Acute Gout

Once diagnosed, there are several therapeutic options available for the treatment of acute gout (12). These therapeutic options are listed in Table 2. If renal, cardiac, and hepatic function are normal, a brief course over 2–7 days of a high-dose NSAID such as indomethacin will rapidly and completely resolve the attack. Unfortunately, most patients encountered in the geriatric practice have underlying renal, cardiac, or hepatic dysfunction such that high-dose NSAID therapy is not the safest option. If the patient presents within 48 hours of the onset of symptoms of acute gout and renal function is normal, oral colchicine loading of 0.6 mg given hourly to a maximum of 6 doses can also rapidly provide relief. This treatment should be discontinued abruptly if diarrhea or GI upset develops. For the older patient with multi-organ dysfunction and a monarticular gouty attack, the safest therapeutic option is an intra-articular injection of a long-acting steroid such as depomethylprednisolone. If the attack is polyarticular, however, local injections are not feasible, and the only safe option for these patients is the use of systemic steroids such as prednisone or its equivalent at an initial dose of 30 mg daily, with a slow taper over 1–2 weeks until the synovitis resolves (13). The use of ACTH for acute polyarticular gout, as pioneered at Mount Sinai Medical Center by Dr. Tsai-Fan Yu, was particularly safe and effective for patients with multiple medical problems, but it is no longer readily available (14, 15). Uric-acid-lowering agents such as probenecid and allopurinol are contraindicated during an acute gouty attack and should not be initiated.

TABLE 2
Therapy of Acute Gout or Pseudogout

NSAIDs
Oral colchicine loading
Intra-articular steroid injections
Systemic steroids

For patients who are at high risk for recurrent gouty attacks, such as those with renal insufficiency or with congestive heart failure on diuretic therapy, prophylactic colchicine 0.6 mg daily should be started during the acute episode and continued in the long term, provided that GI toxicity does not develop. This daily use of low-dose colchicine is ineffective for controlling acute gout, but will markedly reduce the frequency and severity of subsequent gout attacks (16).

Pseudogout

Acute pseudogout is the third most common inflammatory arthritis affecting the elderly. It is caused by an inflammatory reaction generated by the shedding of calcium pyrophosphate crystals into synovial fluid (17). The clinical features that predispose patients to the development of pseudogout are advanced age, acute underlying medical illness, trauma or surgery, hypothyroidism, diabetes, gout, and osteoarthritis.

Attacks of pseudogout can be either monarticular or oligoarticular. The most commonly affected joints are the knees, followed by the shoulders, wrists, and ankles (18). Distal small joint involvement is unusual. The diagnosis of acute pseudogout is established by arthrocentesis, in which examination of the synovial fluid reveals the presence of intracellular calcium pyrophosphate crystals. Chondrocalcinosis, which is a stippled calcification in the cartilages of the knee or the wrist, may be seen in some patients with acute pseudogout, but is not diagnostic and cannot substitute for arthrocentesis (19). The management of acute pseudogout is identical to that of acute gout: NSAIDs, oral colchicine loading, intra-articular steroid injections, and systemic steroids. Prompt treatment of the elderly patient promotes resolution of the inflammatory synovitis and restoration of function.

In summary, while osteoarthritis may be the most frequent cause of joint pain in the elderly, inflammatory arthritis, in the form of RA, acute gout, or pseudogout, is also commonly encountered. These inflammatory diseases are highly responsive to medical therapy. Thus, their recognition and proper management are important, because treatment greatly improves the functional and status quality of life for these patients.

References

1. Wolfe AM. The epidemiology of rheumatoid arthritis: a review. Bull Rheum Dis 1968; 19:518–523.
2. Arnett FC. Revised criteria for the classification of rheumatoid arthritis. Bull Rheum Dis 1989; 38:1–5.
3. Ehrlich GE, Katz WA, Cohen SH. Rheumatoid arthritis in the aged. Geriatrics 1970; 25:103–113.
4. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 1995; 333:142–146.
5. Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. Ann Intern Med 1998; 109:359–363.
6. Van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second line" antirheumatic drugs. Ann Intern Med 1996; 124:699–704.
7. Maini RN. Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple IV infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis. Arth Rheum 1998; 41:1552–1563.
8. Bresnihan B, Alvaro-Garcia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arth Rheum 1998; 41:2196–2204.
9. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor (p75)-FC fusion protein. N Engl J Med; 1997; 337:141–147.
10. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996; 334:1287–1291.
11. McCarty DJ, Hollander JL. Identification of urate crystals in gouty synovial fluid. Ann Intern Med 1961; 54:452–460.
12. Emmerson BT. The management of gout. N Engl J Med 1996; 334:445–451.
13. Alloway JA, Moriarty MJ, Hoogland YF, Nashel DJ. Composition of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. J Rheumatol 1993; 20:111–113.
14. Yu TF. Milestones in the treatment of gout. Am J Med 1974; 56:676–685.
15. Ritter J, Kerr LD, Valeriano-Marcet J, Spiera H. ACTH revisited: effective treatment for acute crystal synovitis in patients with multiple medical problems. J Rheumatol 1994; 21:696–699.
16. Yu TF, Gutman AB. Efficacy of colchicine prophylaxis in gout. Ann Intern Med 1961; 55:179–192.
17. McCarty DJ. Calcium pyrophosphate dihydrate crystal deposition disease: clinical aspects. Clin Rheum Dis 1977; 3:61–89.
18. Dieppe PA, Alexander GJM, Jones HE, et al. Pyrophosphate arthropathy: a clinical and radiologic study of 105 cases. Ann Rheum Dis 1982; 41:371–376.
19. Ellman MH, Levin B. Chondrocalcinosis in elderly persons. Arthritis Rheum 1975; 18:43–47.

Stroke in the Elderly

Mitchell S.V. Elkind, M.D., M.S.

Abstract

Stroke is one of the oldest but least understood diseases, and it is one of the major public health problems facing the elderly. Recent epidemiological investigations have found that the incidence of stroke has been underestimated by about 50%, and that the burden of disease is highest in minority populations. Recent clinical and basic neuroscience research indicates that stroke is neither unpredictable nor irreversible. Many risk factors for stroke are readily identifiable, and evidence-based treatment may be used to reduce the likelihood of stroke among those at risk. Rapid diagnosis and evaluation of stroke and transient ischemic attack and their treatment, including surgery, anticoagulation, antiplatelet and other medical therapies, reduce the chance of recurrence. More aggressive treatment of blood pressure, even among patients who are not necessarily hypertensive, may also reduce the risk of future strokes. Once ischemic stroke has occurred, emergent therapy using thrombolysis may significantly reduce disability, even among the elderly. This review presents an update on definitions of stroke and its subtypes, stroke epidemiology, and the results of recent studies of stroke prevention and acute treatment.

Key Words: Cerebrovascular disorders, clinical trials, epidemiology, elderly, stroke.

STROKE is one of the oldest recognized diseases, but remains one of the least understood. A description of one of the most classic stroke syndromes, the left middle cerebral artery embolism, may have been described in the Bible: "If I forget you, O Jerusalem, let my right hand wither! Let my tongue cleave to the roof of my mouth, if I do not remember you, if I do not set Jerusalem above my highest joy!" (Psalm 137). In some ways, the general understanding of the causes and management of stroke has not progressed much since Biblical times. Most lay people and many physicians believe, for example, that a stroke is a sudden, unpredictable, irretrievable event, like a bolt of lightening blasting a tree. The last two decades of clinical and basic neuroscience research, however, have suggested that stroke is neither unpredictable nor irreversible. This paper focuses on stroke in the elderly, the group most commonly affected by stroke.

Definitions and Subtypes

The generally accepted definition of stroke originates with the World Health Organization (WHO) and dates back to 1980 (1): "Rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin." A transient ischemic attack (TIA) is generally accepted as consisting of the same symptoms, but lasting for up to 24 hours. In the past decade, however, with the advent of improved imaging technologies exquisitely sensitive to the earliest changes of ischemia, such as diffusion-weighted magnetic resonance imaging (MRI), it has become clear that changes consistent with infarction may be seen on MRI in patients whose symptoms last well under 24 hours (Fig. 1). In fact, as many as one-third of patients with symptoms lasting up to one hour have MRI evidence of brain injury (2). The artificial 24-hour line distinguishing stroke from TIA has therefore been called into question. From the neurologist's point of view, the duration of the symptoms is much less important than the cause of the event and what can be done to prevent a future, perhaps more serious — or even fatal — event.

Assistant Professor of Neurology, Columbia University, New York, NY.

Address all correspondence to Dr. Mitchell S.V. Elkind, Neurological Institute, 710 West 168th Street, New York, NY 10032.

Funding: NINDS K23 NS42912

Some of the material was presented at the Mount Sinai School of Medicine Geriatric Medicine Update and Board Review Course, New York, NY, on October 8, 2001.

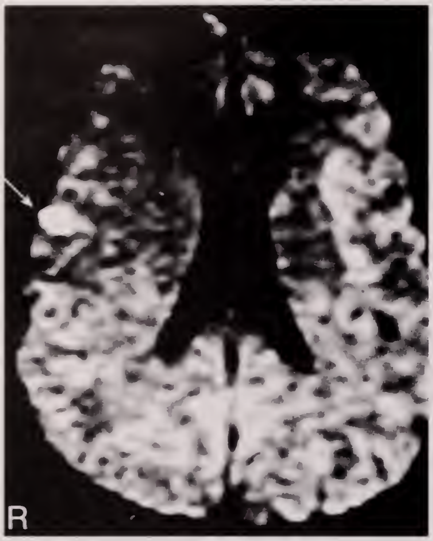

Fig. 1. Abnormal diffusion-weighted MRI scan in a patient with 5 minutes of symptoms. Diffusion-weighted MRI scan in a 54-year-old man with a history of atrial fibrillation who presented with 5 minutes of dysarthria. Neurological examination after symptoms resolved was entirely normal. The MRI shows a small focus of diffusion signal abnormality in the right frontal operculum, consistent with acute ischemia or infarction.

Stroke comes in two major varieties, hemorrhagic and ischemic (Table 1). Approximately 15–20% of strokes are hemorrhagic, divided between subarachnoid hemorrhage and primary intracerebral hemorrhage. The former is classically related to the rupture of berry aneurysms at the base of the brain, while the latter is due to bleeding from "microaneurysms" of smaller blood vessels, presumably weakened by hypertension. While subarachnoid hemorrhage affects people at all ages of life, the elderly can also be affected by intracerebral hemorrhage. One increasingly recognized cause of intracerebral hemorrhage is cerebral amyloid angiopathy, caused by the accumulation of amyloid beta-protein (the same amyloid protein that accumulates in the senile plaques of Alzheimer's disease) in the walls of cerebral vessels (3). Amyloid angiopathy is important because of the high rate of recurrent hemorrhage, as much as 10% per year (4). Subclinical hemorrhages, detected by special gradient echo sequences on MRI scanning, may occur even more frequently (5). Patients with amyloid angiopathy may present with seizures, focal deficits, dementia, or transient attacks not unlike TIAs. Additional causes of cerebral hemorrhage include vascular malformations (arteriovenous malformations and cavernous angiomas), coagulopathies and blood dyscrasias, and neoplasms.

The majority of strokes, approximately 80%, are ischemic (Table 1). Unlike myocardial infarction, for which the etiology in the vast majority of patients is large artery atherosclerosis, only 20% of ischemic strokes are due to large vessel atherosclerosis affecting cerebral blood vessels. Importantly, this 20% is further subdivided between extracranial atherosclerosis ("surgical disease") affecting the carotid or vertebral arteries, and intracranial atherosclerosis, affecting the distal carotid arteries and the vessels of the circle of Willis. Another 20% of ischemic strokes are due to cardiac embolism from a well-defined source of cardiac disease

TABLE 1
Stroke Subtypes

Type	Proportion of All Strokes
Hemorrhagic	15–20%
Subarachnoid hemorrhage	
Intracerebral hemorrhage	
Ischemic	80–85%
	Proportion of ischemic strokes
Extracranial atherosclerosis	10%
Intracranial atherosclerosis	10%
Cardioembolic	20%
Lacunar	20–30%
Cryptogenic	30–40%
Other (dissection, vasculitis, etc.)	<5%

such as valvular heart disease, atrial fibrillation, or mural thrombus. Approximately 20–30% of ischemic strokes are considered "lacunar," due to small vessel disease affecting the thread-like penetrating arteriolar branches of the vessels of the circle of Willis. Lacunar infarcts typically cause a loss of elementary neurological function, causing such conditions as weakness, sensory loss, or unsteadiness, but spare more complex functions such as language and praxis, functions which localize for the most part to the surface gray matter of the hemispheres. Less than 5% of ischemic strokes are due to other specific but unusual causes, like arteritis, dissection, and hypercoagulability. Finally, about 30–40% of ischemic strokes remain unexplained even after a thorough investigation; these are usually termed "cryptogenic." Many of these strokes are thought to be due to emboli from less well-recognized cardiac sources, including patent foramen ovale and aortic arch atheroma.

Stroke diagnosis is fairly straightforward when the symptoms are typical, such as right-sided weakness and nonfluent aphasia occurring together (as in Psalm 137). Many times, however, stroke syndromes are more subtle, and diagnosis may be delayed by hours, days, or even weeks. Common stroke syndromes that do not involve weakness are fluent (or Wernicke's) aphasia and cortical visual loss. Because the inferior division of the middle cerebral artery supplies the lateral temporal and parietal lobes, including Wernicke's area, infarcts in that vessel, usually produced by embolism, may cause a prosodic, fluent speech with multiple paraphasic errors and poor comprehension, while sparing the motor strip in the frontal lobe. The babbling, incomprehensible speech may be misinterpreted as a sign of psychosis, and the patient mistakenly triaged to the psychiatrist. Emboli traveling up the basilar artery may cause significant infarction in bilateral posterior cerebral arteries, causing complete blindness, sometimes with no awareness of the deficit on the part of the patient, due to infarction of both occipital lobes (the "top of the basilar syndrome"). Behavioral abnormalities are common. Memory loss and eye movement abnormalities may also occur, due to the involvement of the medial temporal lobe structures and the midbrain eye movement centers, respectively.

Determination of the stroke subtype requires a thorough diagnostic evaluation. At a minimum, all stroke patients should undergo diagnostic imaging of the brain (computed tomography [CT] or MRI), non-invasive evaluation of the blood vessels of the neck and brain (duplex Doppler ultrasound, transcranial Doppler ultrasound, magnetic resonance [MR] angiography or CT angiography), and echocardiographic evaluation (transthoracic echocardiogram or transesophageal echocardiogram), in addition to routine blood tests and electrocardiography (6). The advantages of MRI scanning include: (a) visualization of the location and extent of ischemia at its very earliest stages; (b) the ability to detect smaller infarcts (particularly in the brainstem, which is difficult to see on CT); and (c) the ability to detect additional infarcts not expected on the basis of the neurological examination, which may indicate a different cause of stroke (Fig. 2). Some medical centers which have advanced MR capability, including MR perfusion scanning, can further use the information provided to determine which patients with acute stroke are likely to benefit from thrombolytic reperfusion therapy. Non-in-

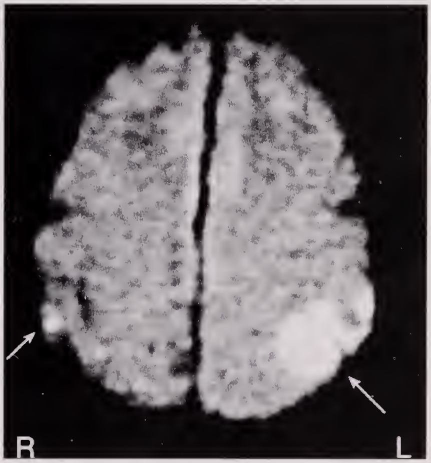

Fig. 2. Bilateral infarcts in setting of myocardial infarction (MI). Diffusion-weighted brain MRI scan in a 72-year-old man with acute aphasia and fluctuating right hemiparesis. Two days before, he had had chest pain for the first time. Emergency echocardiography disclosed anterior wall MI with mural thrombus. Intra-arterial thrombolysis of a branch of the left middle cerebral artery was performed with excellent results. This follow-up MRI shows abnormal signal in the left parietal region consistent with infarction, as well as an additional focus of diffusion signal abnormality in the right parietal region. These bilateral superficial infarcts are most consistent with a "shower" of emboli, and point to a proximal (i.e., cardiac) source of embolism.

vasive vascular imaging is usually adequate to answer most questions about the presence and degree of stenosis in major cerebral vessels, but occasionally conventional angiography is required when non-invasive tests are equivocal. The role of additional diagnostic imaging depends on the results of the initial evaluation and the clinical scenario.

Epidemiology

It would be difficult to overestimate the public health impact of stroke. Stroke is the third leading cause of death and the leading cause of chronic serious disability in the United States. Recent epidemiological studies have provided evidence, moreover, that previous estimates of stroke incidence have underestimated the burden of disease. While earlier data based upon the Framingham study (7), for example, have suggested that there are 500,000 strokes annually in the United States, this data may have failed to take into account the racial and ethnic heterogeneity of the country, and the fact that minority groups are at higher risk of stroke than the predominantly white population studied in Framingham. Estimates based on data from the incidence of stroke in the more representative Cincinnati/Northern Kentucky area (8), for example, indicate that there may be as many as 750,000 strokes annually, an upward revision by 50% over previous estimates.

The impact of ischemic stroke on the population differs according to age, gender, and race-ethnicity, factors generally considered to be risk "markers" for stroke. Age, notably, has been consistently identified as the most important determinant of stroke. For every 10 years after age 55, the stroke rate more than doubles in both men and women (7, 8). Because stroke disproportionately affects the elderly, it is anticipated that the public health burden of stroke will increase in coming decades as the population ages. Overall, men have a greater stroke incidence rate than women by about 30%. Among younger individuals, however, the incidence of stroke among men and women is approximately the same, probably reflecting an increased risk of stroke among young women due to pregnancy and hormonal factors. In the elderly population, women stroke victims outnumber men significantly, despite a lower incidence, because women live longer than men. Stroke, therefore, particularly in the geriatric population, should not be considered simply a disease of men.

Race and ethnicity are also related to stroke incidence and mortality rates. Stroke incidence among blacks in the Cincinnati region is two to four times as high as among whites in Rochester, Minnesota (8). In the Northern Manhattan Stroke Study, blacks and Hispanics each had elevated overall annual age-adjusted relative risks of ischemic stroke compared with whites (2.0 and 3.2 for black men and women, and 1.9 and 2.3 for Hispanic men and women, respectively) (10). Several studies have shown increased mortality rates among blacks and other minority groups. Overall, blacks are more than twice as likely as whites to die of stroke (11). There is some evidence that the increased mortality among blacks is related to socioeconomic and environmental factors, although as much as 50% of the difference in mortality remains unexplained (12).

Risk Factors and Prevention

The majority of strokes occur in people with well-established risk factors (Table 2), and in whom a first stroke can be prevented with the appropriate medications or other treatment

TABLE 2
Stroke Risk Factors

- Non-modifiable Risk "Markers"
  - Age
  - Male gender
  - Race and ethnicity
  - Genetic factors

- Potentially Modifiable Risk Factors
  - Cardiac Risk Factors
    - Well-accepted
      - Atrial fibrillation
      - Myocardial infarction
      - Left ventricular thrombus
      - Valvular heart disease
    - Postulated
      - Patent foramen ovale
      - Atrial septal aneurysm
      - Aortic arch atheroma
      - Mitral annular calcification
      - Mitral valve strands
  - Hypertension
  - Hyperlipidemia
  - Cigarette smoking
  - Diabetes mellitus
  - Physical inactivity
  - Heavy alcohol consumption
  - Drug abuse (especially cocaine)
  - Antiphospholipid antibodies
  - Homocysteine
  - Carotid artery stenosis
  - Transient ischemic attack

(primary prevention; Table 3) (13–23). Because of the limited options for treating patients once stroke has occurred (see below), recognition of risk factors and aggressive prevention efforts remain the best way to reduce the burden of stroke in the U.S. Risk factors can be divided into medical conditions, such as hypertension and diabetes mellitus, and behaviors, including cigarette smoking and physical inactivity. Physicians should attempt to address both medical conditions and behavioral risk factors when discussing stroke risk. Alcohol consumption has a complex relationship with stroke: it appears to increase the risk of hemorrhagic stroke in a linear dose-dependent fashion, but decreases the incidence of ischemic stroke in small doses (up to 2 drinks daily) and increases the risk of ischemic stroke at high doses (5 or more drinks per day). The National Stroke Association guidelines state that drinking in moderation may be protective against stroke, as long as there are no other contraindications (24).

Antihypertensive medications can reduce the risk of stroke in patients with hypertension, and warfarin can reduce the risk in patients with atrial fibrillation. Treatment of hyperlipidemia reduces the risk of a first stroke, though not to the same degree that it reduces the risk of a first myocardial infarction (MI), possibly reflecting the heterogeneity of causes of stroke compared with the causes of MI.

Surgical carotid endarterectomy reduced the risk of a first stroke among patients with asymptomatic carotid stenosis of at least 60% in the Asymptomatic Carotid Atherosclerosis Study (ACAS) (23). The benefit was of moderate clinical significance, however, reducing the incidence of stroke from about 2% to 1% annually, reflecting the low rate of stroke in the asymptomatic patient. Complication rates were higher among women than men (3.6% vs. 1.7%), and an independent, clinically significant benefit was not found in women. Patients aged 80 and older and those with symptomatic cardiac disease were not eligible for the study, so the procedure should not be routinely recommended to those over the age limit used in the study, and particularly not to those with concomitant cardiac disease. In addition, the procedure should only be performed by an experienced surgeon with a demonstrated perioperative complication rate below 3%. The role of carotid angioplasty and stenting in this population also remains unproven. Table 3 lists several interventions proven in randomized, clinical trials in recent years to prevent a first ischemic stroke.

Once a stroke has occurred, many of the same risk-factor-modifying therapies shown to be effective in primary prevention are likely to continue to be of benefit in preventing recurrence (secondary prevention; Table 4). Moreover, investigators have recently shown that

TABLE 3

Primary Prevention of Ischemic Stroke in the Elderly

Risk Factor	**Treatment**	**Trial (Reference)**
Hypertension	Antihypertensive	SHEP (13), others
Myocardial infarction	HMG CoA reductase inhibitors	4S (14), CARE (15), LIPID (16)
Hyperlipidemia	HMG CoA reductase inhibitors	WOSCOPS (17)
Atrial fibrillation	Warfarin	AFASAK1 (18), SPAF (19), BAATAF (20), SPINAF (21)
	Aspirin	SPAF (19)
Diabetes mellitus	Ramipril (ACE inhibitor) Glycemic control	HOPE
Asymptomatic carotid stenosis	Carotid endarterectomy	ACAS (24)
Behavioral risk factors (smoking, heavy alcohol consumption, drug abuse, physical inactivity, etc.)	Stop smoking; limit or eliminate alcohol consumption; avoid drug abuse; exercise, etc.	—

HMG CoA=3-hydroxy-3-methyl glutaryl-coenzyme A; ACE=angiotensin-converting enzyme; SHEP=Systolic Hypertension in the Elderly Prevention Trial; 4S=Scandinavian Simvastatin Survival Study; CARE=Cholesterol and Recurrent Events Trial; LIPID= Long-Term Intervention with Pravastatin in Ischaemic Disease; WOSCOPS=West of Scotland Coronary Prevention Study; AFASAK=Atrial Fibrillation, Aspirin and Anticoagulation Study; SPAF=Stroke Prevention in Atrial Fibrillation; BAATAF= Boston Area Anticoagulation Trial in Atrial Fibrillation; SPINAF=Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study; HOPE=Heart Outcomes Prevention Evaluation; ACAS=Asymptomatic Carotid Atherosclerosis Study.

TABLE 4

Secondary Prevention of Ischemic Stroke in the Elderly

Risk Factor	Treatment	Trial (Reference)
Hypertension (and consider in all patients, with or without hypertension)	Perindopril (ACE inhibitor) plus indapamide (diuretic) or ramipril	PROGRESS (25) HOPE (26)
Atrial fibrillation	Warfarin	EAFT (22)
Other definite cardioembolic source	Warfarin	—
No cardioembolic source	Antiplatelet therapy Warfarin*	Multiple (see text) WARSS (40)
Symptomatic carotid stenosis	Carotid endarterectomy	NASCET (27)
Hyperlipidemia	HMG CoA reductase inhibitors	—
Diabetes mellitus	Glycemic control	—
Behavioral risk factors (smoking, heavy alcohol consumption, drug abuse, physical inactivity, etc.)	Stop smoking; limit or eliminate alcohol consumption; avoid drug abuse; exercise, etc.	—

*In some cases, even in patients without cardioembolic source, such as those with severe intracranial stenosis, patent foramen ovale, aortic atheroma, or recurrent strokes despite antiplatelet therapy, anticoagulation with warfarin remains a reasonable alternative treatment (see text).

ACE=angiotensin-converting enzyme; HMG CoA=3-hydroxy-3-methyl glutaryl-coenzyme A; HOPE=Heart Outcomes Prevention Evaluation; PROGRESS=Perindopril Protection Against Recurrent Stroke Study; EAFT=European Atrial Fibrillation Trial; WARSS=Warfarin Aspirin Recurrent Stroke Study; NASCET=North American Symptomatic Carotid Endarterectomy Trial.

among patients with a first stroke or TIA, even in the absence of documented hypertension, treatment with antihypertensive therapy may reduce the risk of a recurrent event. Once a patient has had a stroke, it has been suggested, even a blood pressure traditionally defined as normal may be too high. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial (25), for example, an international, randomized, double-blind, placebo-controlled trial of antihypertensive therapy among 6,105 patients with a history of stroke (hemorrhagic or ischemic) or transient ischemic attack within the past 5 years, patients were enrolled independent of hypertension status, and 52% were considered non-hypertensive (i.e., systolic BP ≤ 160 and diastolic BP ≤ 90 mm Hg). The mean blood pressure among non-hypertensives was 136/79 at baseline. Active treatment with the combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril 4 mg daily and the diuretic indapamide 2.5 mg daily led to a reduction in blood pressure of 12/5 mm Hg compared with placebos, and a statistically significant 43% reduction in stroke risk. The combination therapy provided a benefit of a similar magnitude among both hypertensive and non-hypertensive patients. The role of ACE inhibitor therapy in stroke prevention is also supported by the Heart Outcomes Prevention Evaluation (HOPE) trial (26), which enrolled patients with a history of stroke, MI or diabetes, independent of blood pressure status, and randomized patients to the ACE inhibitor ramipril or placebo. Approximately 10% of patients had a history of stroke. In that study, despite a very small mean blood pressure reduction of 3/2 mm Hg, there was a statistically significant 22% risk reduction in vascular events. Trials are ongoing to determine whether lipid-lowering therapy with statins can reduce the risk of recurrent stroke in patients with normal or near-normal lipid levels (and free of concomitant heart disease) in the same way that such treatment reduces the risk of recurrent cardiac disease.

In patients with symptomatic carotid stenosis, carotid endarterectomy substantially reduces the risk of recurrent stroke. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), surgery reduced the 2-year risk of recurrent stroke from 26% with medical management alone to 9% (27). The available data suggest that there is no advantage to angioplasty and stenting over carotid surgery for the symptomatic patient (28, 29). While coronary angioplasty has clear advantages over bypass surgery, including avoidance of a very painful sternotomy, obtaining surgical access to the carotid artery involves a small incision and minimal dissection in the neck. Patients do not have significant pain, do not require prolonged rehabilitation, and may be able to leave the hospital the day after the procedure. Carotid endarterectomy may even be performed for some patients using local anesthesia. Until large, randomized trials demonstrate its value, carotid angioplasty and stenting should be considered an experimental procedure, and endarterectomy the procedure of choice. In certain select settings, however, angioplasty offers advantages over endarterectomy. In patients with surgically inaccessible disease due to a high carotid bifurcation or intracranial atherosclerosis, for example, angioplasty may be the only option.

In addition to management of medical and behavioral risk factors, and surgery when indicated, antiplatelet therapy reduces the risk of recurrent stroke after a first event. Studies have consistently demonstrated the benefit of aspirin, the mainstay of antiplatelet treatment (30, 31). The optimal dosage of aspirin remains controversial, though recent trial data provide support for doses of 50–325 mg (32, 33). Gastrointestinal side effects are less frequent with lower aspirin doses. In a meta-analysis (34) of randomized data among more than 10,000 patients with cerebrovascular disease, investigators found that 37 future vascular events per 1,000 patients treated could be prevented ($p<0.000005$) with aspirin. The relative odds reduction was similar for those presenting with completed stroke (23%) versus TIA (22%) (34), again disparaging the notion of a strict demarcation between the two.

The past decade has witnessed the development of several new antiplatelet agents that can be used in place of or in addition to aspirin. Ticlopidine and clopidogrel, related thienopyridine-derivative compounds that inhibit adenosine diphosphate-induced platelet aggregation, are both effective (35). Ticlopidine was more effective than aspirin at preventing stroke among those with TIA or minor stroke in the Ticlopidine Aspirin Stroke Study (TASS), though its benefit in reducing a composite endpoint of stroke, MI, or vascular death was less clear (36). Side effects with ticlopidine also limit its use; they include diarrhea in more than 10% and severe neutropenia in approximately 1% of patients. Considering patients with a history of MI, stroke, and peripheral arterial disease as a group, clopidogrel, a compound approved by the FDA in 1998 and related to ticlopidine, was marginally superior to aspirin in preventing a composite outcome event; absolute risk reduction with clopidogrel was 0.5%, from 5.8% to 5.3% annual risk ($p=0.05$). There was statistically significant heterogeneity among the different patient categories in the population, however, and for the approximately 6,000 patients with cerebrovascular disease, clopidogrel was comparable to aspirin (37). Clopidogrel is generally well tolerated, although reports of thrombotic thrombocytopenic purpura have led some to recommend routine monitoring of platelet levels after initiating therapy (38).

Combination therapy with two antiplatelet agents is an emerging strategy that has been tested in the European Stroke Prevention Study 2 (ESPS 2). It utilized a factorial design comparing placebo, aspirin 25 mg twice daily, a new extended-release formulation of dipyridamole 200 mg twice daily, and the combination of aspirin and dipyridamole at these doses (39). The combined therapy arm had the greatest benefit, with reduction in risk of stroke essentially additive between the single treatment arms (risk reduction of 37%, $p<0.001$, with combined treatment compared to placebo). The combination of other antiplatelet agents with distinct mechanisms of action, such as clopidogrel and aspirin, is currently being tested in stroke patients in other studies, and may play an increasing role in the future.

The role of warfarin in secondary stroke prevention among patients without definite cardioembolism has recently been revised to some extent on the basis of the Warfarin Aspirin Recurrent Stroke Study (WARSS) results (40). This study was designed to test whether warfarin (international normalized ratio [INR] 1.4–2.8) is more effective than aspirin (325 mg) in preventing recurrent stroke. The study was a randomized, blinded trial for patients who had had an ischemic stroke within 30 days prior to randomization, without severe carotid stenosis or definite cardioembolic source (i.e., patients with aortic atheroma or patent foramen ovale were eligible for enrollment). After 2 years of follow-up with 2,206 patients, there was no statistically significant advantage of warfarin over aspirin. Patients were also stratified by etiologic subtype, and in no group was warfarin more efficacious than aspirin. Notably, warfarin was not less safe than aspirin (annual risk of major hemorrhage: 2.2% on warfarin and 1.5% on aspirin, $p=0.10$). Warfarin remains a reasonably safe alternative for some patients with ischemic stroke, such as those with severe intracranial stenosis; cryptogenic superficial, cortical infarction with patent foramen ovale; mobile aortic atheroma; or recurrent strokes despite antiplatelet therapy. Its utility in the majority of stroke patients, however, remains unproven.

Acute Treatment for Stroke in the Elderly

As noted briefly above, stroke is not necessarily an irreversible event. Stroke evolves over a period of time, with the time required for irreversible neuronal injury dependent upon the degree of the reduction in blood flow to the brain. The longer blood flow is impaired and the lower the blood flow, the more likely it is that irreversible brain injury will occur. These facts have clinical implications. The first is that early blood flow restoration is more likely to salvage brain tissue. Thus, therapies designed to restore blood flow, such as tissue-type plasminogen activator (rt-PA), should be given as quickly as possible. The pivotal trial that demonstrated the benefit of rt-PA for acute ischemic stroke, the National Institute of Neurological Disorders and Stroke (NINDS) trial, showed that there was a statistically significant benefit in favor of rt-PA over placebo for patients treated within 3 hours of symptom onset (41). The proportion of patients that achieved functional independence in activities of daily living at 3 months after stroke was 50% in the group treated with rt-PA compared with 38% in the placebo group. Further analyses of the data from the study have shown that the earlier thrombolytic therapy was administered in the pivotal NINDS rt-PA study, the more likely patients were to have a favorable outcome, a point which was not recognized at the time tPA was first approved for stroke (42).

An understanding of the pathophysiology of stroke also leads to the recognition that levels of cerebral blood flow must be maintained as high as possible in the setting of acute ischemic stroke. Under ordinary circumstances (i.e., in the healthy brain not undergoing ischemia), cerebral arterioles are able to maintain adequate cerebral blood flow throughout a wide range of systemic blood pressures via the process of autoregulation. In the setting of stroke, however, cerebral autoregulation fails and collateral blood flow through the circle of Willis and other routes becomes heavily dependent upon systemic blood pressure. Thus, attempts to reduce blood pressure, though well intended by the emergency room physician most often accustomed to treating cardiac ischemia, may actually exacerbate brain ischemia and worsen an infarct. Some recent data even suggest that hypertensive therapy may be of benefit in limiting cerebral injury after stroke (43). Hypertension should be avoided, however, in patients who have received thrombolytic therapy, as it may increase the risk of hemorrhagic conversion in this setting. General principles for the management of acute ischemic stroke are given in Table 5.

The use of rt-PA for acute ischemic stroke continues to encounter resistance in some quarters, due to the increased risk of hemorrhagic conversion associated with rt-PA use after ischemic stroke. In the NINDS trial, there was a 6.4% risk of symptomatic hemorrhage within 36 hours among those treated with rt-PA, compared with a 0.6% risk among those treated with placebo (41). Not surprisingly, this tenfold increase in risk has scared many away from using rt-PA for ischemic stroke. The overall rate of neurologic worsening in 36 hours, however, was in fact similar between the two groups (17.4% in the rt-PA group and 18.3% in the

TABLE 5

Management of Acute Ischemic Stroke

1. Determine time window (time since patient was last known to be normal)
    - 0–3 hours: Consider intravenous rt-PA 0.9 mg/kg
    - 3–6 hours: Consider intra-arterial thrombolysis
    - > 6 hours: Aspirin 325 mg and consider addition of heparin 5000 units subcutaneously twice daily*
2. General principles of management
    - ABC's (Airway, Breathing, Circulation)
    - Avoid hypotension
        - For patients who receive thrombolysis, maintain systolic blood pressure <180 mm Hg and diastolic blood pressure < 105 mm Hg
    - Avoid hyperglycemia (goal blood sugar < 180)
    - Avoid hyperthermia/treat fever and infections
    - Avoid free water/hydrate with normal saline
    - Treat seizures if they occur
    - Consider neurosurgical intervention in setting of cerebellar infarction with edema / hydrocephalus or massive hemispheric infarction with edema / risk of herniation

*In some situations, including cardioembolic stroke or severe arterial stenosis, adjusted-dose unfractionated heparin may be considered the best treatment, according to the discretion of the treating physician.

See text for references.

rt-PA=recombinant tissue-type plasminogen activator placebo group). This perhaps surprising result is due to the fact that other adverse consequences of having a stroke — brain swelling and herniation, recurrent ischemia, seizures, and others — occurred more frequently in those who did not receive rt-PA. In other words, hemorrhage is not the only adverse consequence of ischemic stroke. Also, those patients who suffered symptomatic hemorrhages were those who initially presented with large strokes; these patients may have been likely to go on to hemorrhage or to have a poor prognosis even in the absence of rt-PA. Several phase IV studies have since confirmed the generalizability of the benefits of rt-PA to the community at large (44).

The reluctance to use rt-PA is particularly strong, however, in treating elderly patients, as the elderly are thought to be at higher risk of hemorrhage after thrombolysis than are younger patients. Older patients also have a worse overall prognosis after stroke than do younger patients. A secondary analysis of the NINDS trial, however, found that elderly patients do not have a higher risk of converting to symptomatic hemorrhage, and that, on average, they demonstrate the same benefit from rt-PA as do younger patients (45). There is, therefore, no *a priori* reason to exclude the elderly patient from thrombolytic treatment on the basis of age alone. Because the benefit of treatment is primarily to increase the long-term likelihood of independence, however, it would not be unreasonable to limit treatment to those who were previously independent. The elderly, demented nursing home resident, for instance, will not be restored to independence as a result of thrombolytic therapy.

Most patients will not be treated within 3 hours of onset of their strokes. Nationwide, only about 1–2% of stroke patients are treated with thrombolytic therapy. Studies that have employed intravenous thrombolytic agents administered beyond three hours, moreover, have not found a benefit in functional outcome despite an increased risk of hemorrhage (46, 47). A pivotal clinical trial (48) using intra-arterial thrombolysis with prourokinase among patients with hemispheric infarcts treated up to 6 hours after symptom onset, however, found a benefit in terms of functional outcome at 3 months, but this form of aggressive treatment is only available in selected centers.

Beyond the 6-hour time window, except in rare cases, antiplatelet therapy and subcutaneous heparin at a dose of 5000 units twice daily remain the mainstays of treatment. Neither adjusted-dose unfractionated heparin nor heparinoids have been convincingly shown to be of benefit in acute stroke treatment, despite a long history of use. In the International Stroke Trial (IST) (49), 19,435 patients with acute ischemic stroke were randomized in a 3 × 2 factorial design study to receive either heparin 12,500 units subcutaneously twice daily, heparin 5000 units subcutaneously twice daily, or no heparin; and aspirin 300 mg daily or no aspirin. There were thus 6 possible allocation groups. At 6 months, after adjustment for severity of the stroke, there was in the aspirin group (vs. placebo, independent of heparin) a statistically significant reduction of 14 per 1000 treated in those who died or were left dependent. Other trials of aspirin in acute stroke have provided similar results (50), suggesting that aspirin is not only an effective long-term stroke preventative therapy, as discussed above, but that it might have a role to play in acute stroke management as well. There was some evidence from the IST to suggest that the combination of aspirin and low-dose subcutaneous heparin (5000 units twice daily) provided the best short-term outcome, though this was based on subgroup analysis.

Conclusions

Stroke continues to be one of the major public health problems facing the elderly today. The past two decades of investigations into stroke imaging, epidemiology, pathophysiology, and treatment have fundamentally changed the way in which stroke is viewed by neurologists. Stroke can be prevented in many cases, and successfully treated in others when it occurs. Crucial to our success in doing so, however, is improved education of patients and physicians, the rapid and thorough evaluation of patients with symptoms of TIA and stroke, and further research into causes and treatment of stroke.

References

1. Aho K, Harmsen P, Hatano S, et al. Cerebrovascular disease in the community: results of a WHO collaborative study. Bull WHO 1980; 58:113–130.
2. Kidwell CS, Alger JR, Di Salle F, et al. Diffusion MRI in patients with transient ischemic attacks. Stroke 1999; 30(6):1174–1180.
3. Sacco RL. Lobar intracerebral hemorrhage. N Engl J Med 2000; 342:276–279.
4. O'Donnell HC, Rosand J, Knudsen KA, Furie, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med 2000; 342: 240–245.

5. Greenberg SM, O'Donnell HC, Schaefer PW, Kraft E. MRI detection of new hemorrhages: potential marker of progression in cerebral amyloid angiopathy. Neurology 1999; 53:1135 – 1138.
6. Adams HP, Jr, Brott TG, Crowell RM, et al. Guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 1994; 25:1901 – 1914.
7. Wolf PA, D'Agostino RB, O'Neal MA, et al. Secular trends in stroke incidence and mortality: the Framingham Study. Stroke 1992; 23:1551 – 1555.
8. Broderick J, Brott T, Kothari R, et al. The Greater Cincinnati/Northern Kentucky Stroke Study. Preliminary first-ever and total incidence rates of stroke among blacks. Stroke 1998; 29:415 – 421.
9. Brown RD, Whisnant JP, Sicks RD, et al. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke 1996; 27:373 – 380.
10. Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. Am J Epidemiol 1998; 147:259 – 268.
11. Howard G, Anderson R, Sorlie P, et al. Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks: the National Longitudinal Mortality Study. Stroke 1994; 25:2120 – 2125.
12. Giles WH, Kittner SJ, Hebel JR, et al. Determinants of black-white differences in the risk of cerebral infarction. Arch Intern Med 1995; 155:1319 – 1324.
13. SHEP Cooperative Research Group. Prevention of stroke by hypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991; 265:3255 – 3264.
14. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol-lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383 – 1389.
15. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. N Engl J Med 1996; 335:1001 – 1009.
16. The Long-Term Intervention with Pavastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339:1349 – 1357.
17. Sheperd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333:1301 – 1307.
18. Petersen P, Boysen G, Gotfredsen J, et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK Study. Lancet 1989; 1:175 – 179.
19. [Stroke Prevention in Atrial Fibrillation (SPAF) Investigators.] Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991; 84:527 – 539.
20. [Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators.] The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990; 323:1505 – 1511.
21. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med 1992; 327:1406 – 1412.
22. European Atrial Fibrillation Trial Study Group. Secondary prevention in nonrheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993; 342:1255 – 1262
23. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995; 273:1421 – 1428.
24. Stroke Prevention Advisory Board. National Stroke Association Stroke Prevention Guidelines. J Stroke Cerebrovasc Dis 1998; 7:162 – 164.
25. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. PROGRESS Collaborative Group. Lancet 2001; 358:1033 – 1041.
26. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342: 145 – 153.
27. [North American Symptomatic Carotid Endarterectomy Trial Collaborators.] Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325:445 – 453.
28. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001; 357:1729 – 1737.
29. Sacco RL. Extracranial carotid stenosis. N Engl J Med 2001; 345:1113 – 1118.
30. The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 1978; 299:53 – 59.
31. The SALT Collaborative Group. Swedish Aspirin Low-dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. Lancet 1991; 338:1345 – 1349.
32. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991; 54:1044 – 1054.
33. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991; 325:1261 – 1266.
34. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy — I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308:81 – 106.
35. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989; i:1215 – 1220.
36. Hass WK, Easton JD, Adams HP, Jr., et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. N Engl J Med 1989; 321:501 – 507.
37. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348:1329 – 1339.
38. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000; 342:1773 – 1777.
39. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurolog Sci 1996; 143:1 – 13.
40. Mohr JP, Thompson JLP, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001; 345:1444 – 1451.
41. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581 – 1587.

42. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology 2000; 55:1649–1655.

43. Rordorf G, Koroshetz WJ, Ezzeddine MA, et al. A pilot study of drug-induced hypertension for treatment of acute stroke. Neurology 2001; 56:1210–1213.

44. Albers GW, Bates VE, Clark WM, et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. JAMA 2000; 283:1145–1150.

45. The NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. Stroke 1997; 28:2119–2125.

46. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998; 352:1245–1251.

47. Clark WM, Wissman S, Albers GW, et al. recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. JAMA 1999; 282:2019–2026.

48. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II Study: a randomized controlled trial. JAMA 1999; 282:2003–2011.

49. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. Lancet 1997; 349:1569–1581.

50. CAST: a randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997; 349:1641–1649.

Overview:

Depression in the Elderly

Michael Serby, M.D.[1], and Mi Yu, M.D., Ph.D.[2]

Abstract

Depression in the elderly population is a major public health problem. It has a high prevalence, is frequently co-morbid with medical illnesses, impacts negatively on quality of life, increases the number of visits to different medical services, and carries a high risk of suicide, especially in men. Imaging studies have increased our understanding of the biological mechanisms of depression in the elderly. Depression is sometimes difficult to diagnose in the elderly. It should be differentiated from apathetic states ("negative syndrome"), and its treatment requires knowledge of specific physiological changes that occur in this age group. Geriatric depression is more somatic and less ideational than depression in other age groups. Acute treatments with various antidepressant medications, augmentation strategies, electroconvulsive treatments, and psychotherapy must be coupled with maintenance strategies to prevent recurrences, which are common.

Key Words: Depression, elderly, diagnosis, treatment.

DEPRESSION IN PEOPLE aged 65 years and older is a major public health problem (1, 2). It causes suffering to many who go undiagnosed and untreated, and it burdens families and institutions that provide care for the elderly, by disabling those who might otherwise be independent and productive (2). Utilization of medical outpatient services increases. Depressed older people consult their general practitioner two to three times more often than nondepressed elders (3). Early recognition, diagnosis, and initiation of treatment for depression in older people present opportunities for improving their quality of life, preventing suffering or premature death, and maintaining optimal levels of function and independence (2).

Epidemiology

Prevalence

The prevalence of major depression in the geriatric population, regardless of ethnicity, is 1.4% in women, 0.4% in men, and 1% overall. Approximately 2% of the elderly suffer from dysthymic disorder, and 4% have an adjustment disorder with depressed mood. Approximately 15% have depressive symptoms that do not meet criteria for a specific depressive syndrome. Alexopoulos (4) has stated, "In older patients treated in primary care settings, depression was identified in 17–37% of patients; 30% of these patients had major depression and the remainder had a variety of depressive syndromes that could benefit from medical attention. In medically hospitalized patients, major depression occurs in 11%, and less severe yet clinically significant depressive symptoms are identified in 25% of the population. The corresponding figures for patients treated in long-term care settings are 12% and 30%, respectively."

Risk Factors

Women have higher rates of all types of depression than do men (2). The major social and demographic risk factors for depression in the elderly are: female gender; single status, particularly for the widowed; stressful life events; and lack of a supportive social network (5).

Mortality

Mortality rates by suicide and other causes are higher among elderly persons with depression than their nondepressed counterparts (5). Depressive symptoms are found to be an independent risk factor for mortality in community-residing older adults (6). The increased rates of suicide (1, 3, 7) in the elderly may contribute to this latter outcome.

---

[1] Associate Chairman, and [2] Fellow in Geriatric Psychiatry, Department of Psychiatry, Beth Israel Medical Center, New York, NY.

Address all correspondence to Michael Serby, M.D., Department of Psychiatry, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY 10003.

This work is based on a presentation at the Geriatric Medicine Update and Board Review at the Mount Sinai School of Medicine, New York, NY on October 5–8, 2001.

The elderly age group has the highest risk for suicide of all age groups (4, 5, 8, 9). The major social and demographic risk factors for suicide among the elderly are: old age, male gender, white race and unmarried status (2, 4, 9, 10). The suicide rate for white American men 65 years and older is five times that of the general population (4, 11, 12). Generally, these suicidal patients are suffering from their first episode of major depression, which is moderately severe, yet the depressive symptoms have gone unrecognized and untreated (5).

Most elderly persons who commit suicide communicate their suicidal thoughts to family or friends before killing themselves (4). More than three-fourths of these individuals visit a primary care physician about general medical problems and somatic complaints less than one month prior to their suicide (2, 5, 12–14), 39% the week before (2). Although it would not be feasible to screen all older primary care patients for suicidality, physicians should ask about suicidal thoughts in all older patients who present with symptoms of depression (2). There should be no reluctance to question patients about suicidal ideation, because there is no evidence that such questions can increase the likelihood of suicidal behavior (4).

DSM-IV Diagnosis

Despite an intensive search for biological and structural correlates of late-life depression, no specific diagnostic test can be recommended for clinical practice (5). Tables 1 and 2 list the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) symptoms of major depressive disorder and dysthymic disorder (15). The "depressive disorder not otherwise specified" category includes disorders with depressive features that do not meet the criteria for major depressive disorder, dysthymic disorder, adjustment disorder with depressed mood, and adjustment disorder with mixed anxiety and depressed mood. Other DSM-IV disorders such as adjustment disorder, bereavement, mood disorder due to general medical condition, substance-induced mood disorder, sleep disorder, hypochondriasis, and even psychotic disorders, may be manifested by a depressive picture.

TABLE 1
Symptoms of Major Depression

1. Depressed mood
2. Loss of interests
3. Weight loss or appetite change
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Loss of energy or fatigue
7. Feelings of worthlessness or guilt
8. Difficulty with concentration or decision making
9. Recurrent thoughts of death or suicide

TABLE 2
Symptoms of Dysthymic Disorder

1. Depressed mood
2. Poor appetite or overeating
3. Insomnia or hypersomnia
4. Low energy or fatigue
5. Low self-esteem
6. Difficulty with concentration or decision making
7. Feelings of hopelessness

Clinical Characteristics of Elder Depression

What often makes depression in the elderly so insidious is that neither the victim nor the health care provider may recognize its symptoms in the context of the multiple physical problems of many elderly people. Depressed mood, the typical signature of depression, may be less prominent than other depressive symptoms such as loss of appetite, sleeplessness, anergia, and loss of interest (2, 5). Elderly depressed persons are more likely than younger depressed adults to express somatic complaints, fail to report feelings of guilt, and minimize the presence of depressed mood ("masked depression") (4). That is why it is prudent to inquire about satisfaction with life, hopefulness, worthlessness, helplessness, preoccupations, motivations, worrying, etc. when diagnosing depression in the elderly, even if the patient denies feeling depressed. Hypochondriacal symptoms occur in approximately 65% of elderly persons with depression (4). Thus, it may be said that geriatric depression is less ideational and more somatic.

Elderly depressed persons are more likely than younger persons to have psychotic (delusional) depression. The usual themes of depressive delusions are guilt, hypochondriasis, nihilism, persecution, and sometimes jealousy (4).

When dealing with the elderly age group, both clinicians and patients may incorrectly attribute depressive symptoms to the aging process (5). It has been repeatedly stressed that depression is a clinical syndrome, not part of normal aging (3, 5, 16).

Central Nervous System Changes

Late-onset depression often is associated with a variety of brain abnormalities, such as ventriculomegaly, and significant reduction of brain volume and white-matter hyperintensities, most commonly involving selective prefrontal, superior temporal, and anterior parietal cortex (2, 17–19). Reductions in global cortical cerebral blood flow and cerebral metabolic rate have been reported in late-life depression (17, 20–22). Postmortem studies demonstrate a reduction in thickness and size of neurons and neuronal cell bodies, and decrease in glial density in the orbital frontal cortex (23).

Geriatric depression is often co-morbid with vascular disorders and is accompanied by lesions in the basal ganglia and prefrontal areas of the brain (2). Available evidence suggests that depression accompanying cerebrovascular disease is more likely to be associated with frontal/subcortical dysfunction than with damage to other regional brain areas (24).

Serotonin (5-HT) neurotransmission has recently become a focus of attention in depression research. Interestingly, limited research involving the 5-HT system in human aging has provided some evidence of reductions of 5-HT binding with advanced age (22, 25–27). No clear pattern of the effects of aging on overall 5-HT activity (e.g., transmitter and metabolite concentrations and turnover) could be identified (22), although there was a suggestion of increased 5-HT turnover in the elderly (28, 29). Serotonin dysregulation may be associated with geriatric major depressive disorder (22).

Medical Co-morbidities

Late-onset depression is associated with a lower frequency of family history of depression but a higher frequency of cognitive impairment, cerebral atrophy, deep white matter changes, recurrences, medical co-morbidity, and mortality than in younger patients (4, 5). Medical co-morbidity includes cancer, cardiovascular disease, neurological disorders, various metabolic disturbances, arthritis, and sensory loss (5).

In clinical populations of elderly persons, depression occurs in approximately 20–25% of patients suffering a stroke (4), with a prevalence of up to 50% within the first month after a stroke (24). Cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes (4). Basal ganglia and left-hemisphere lesions, especially those close to the frontal pole, are most frequently associated with post-stroke depression. Cortical and lacunar infarcts have the highest co-morbidity with depression (4).

The prevalence of significant levels of depression in Parkinson's disease (PD) is estimated to be 40%. The relationship between mood and motor phenomena in PD is complex. PD can be misdiagnosed as a primary depressive illness, and concomitant depression may go unrecognized in PD patients. It can be difficult to tease apart which clinical phenomena are related to primary motor dysfunction as opposed to primary depression. For example, the slowed movement of bradykinesia and masked faces in PD are well-recognized components of depression, usually described as psychomotor retardation and restricted affect. This can be observed in PD patients with depression who are receiving treatment. Motor improvement with antiparkinsonian medications is not associated with improved mood (30). Electroconvulsive therapy (ECT) can effectively treat both depressive and psychotic symptoms with concurrent enhancement of motor function in Parkinson's disease patients (31), with motor dysfunction generally improving prior to improvement in mood (32).

Depressive manifestations of various intensities occur in approximately 50% of demented patients; major depression occurs in 15–20% of patients with Alzheimer's disease (4). Some depressed elderly patients develop a dementia syndrome that resolves either completely or partially after remission of depression. Terms such as "pseudodementia," "dementia of depression," or "depression with reversible dementia" have been used to describe this transient cognitive syndrome. Depressed elderly patients who have only partial cognitive improvement after the amelioration of depression usually have an early-stage dementing disorder; their cognitive symptoms may be exacerbated when the depressive syndrome is superimposed (2, 4).

Many symptoms and signs of the depressive syndrome overlap with manifestations of medical and neurological diseases. For example, insomnia, fatigue, agitation, and psychomotor retardation can be caused by many medical illnesses and dementing disorders (4). Apathy, part of a frontal lobe syndrome, may be misidentified as the retardation characteristic of depression. Apathy can present in a variety of medical and psychiatric disorders, including PD, delirium, dementia, schizophrenia, "apathetic hyperthyroidism," and amphetamine or cocaine withdrawal, or as an independent syndrome (33), sometimes indistinguishable from negative symptoms in schizophrenia (flat affect, poverty of ideas, asociality, inactivity) (34).

Distinguishing between such symptoms as affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, and inattentiveness, and depression is necessary to be able to predict the course of the disease and plan for treatment and rehabilitation. Diseases in which negative symptoms are present may or may not be co-morbid with depression. However, both negative symptoms and depression can significantly affect the recovery and functioning of these patients. Clinically, negative and depressive symptoms overlap significantly. Even though it might be difficult to distinguish between them, adequate management is possible only if these two syndromes are correctly diagnosed (34).

Treatment

Treatment of depression can reduce excessive levels of disability and result in improved levels of functioning (2). Psychotherapy, drug therapy, or ECT used alone or in combinations is effective in the treatment of geriatric depression (4, 5). The effectiveness of such treatments for less severe depression, which may negatively affect quality of life, is unclear. These treatments can be associated with increased risk of co-morbid medical illnesses (5).

The goals of treatment are to achieve remission of symptoms, prevent relapse and recurrence, improve quality of life and functional capacity, and perhaps to improve medical health status and decrease health care costs and mortality (2, 5).

Pharmacotherapy

Physiology. From roughly age 40 onward, changes in body composition, renal function, cardiac output, and other physiologic processes begin to accelerate, resulting in an age-related increase in the variability of drug disposition and response, and an overall gradual diminution in the rate of drug elimination. Thus, it takes longer to achieve steady-state plasma concentrations and to wash drugs out of older patients. The variability in pharmacokinetics is such that dosing for elderly patients is less predictable than for younger adults. Recommended initial doses for all antidepressants are lower for the elderly, although optimal doses may not differ from those for younger patients once dosing is individualized (35).

Antidepressants. Selective serotonin re-uptake inhibitors (SSRIs) are a common, preferred treatment for acute episodes of depression in elderly patients, because of their favorable side-effect profile, relative safety in overdose, ease of use, smaller dosage adjustment, and greater acceptance (2, 16, 36). Unlike a tricyclic antidepressant (TCA), an SSRI will have minimal cardiovascular effects and will not worsen cognition, since it has less anticholinergic toxicity (2, 16). Common complaints linked to SSRIs include nausea, diarrhea, insomnia, sedation, headache, agitation, and anxiety (2, 16). More problematic adverse effects in older patients include SSRI-induced syndrome of inappropriate antidiuretic hormone secretion, extrapyramidal symptoms (EPS), and bradycardia (2).

The risk of developing hyponatremia while on an SSRI seems to be higher with increasing age, female sex, previous history of hyponatremia and the concomitant use of other medications known to cause hyponatremia. In the majority of cases, SSRI-associated hyponatremia is transient, mild and asymptomatic. SSRI-induced hyponatremia may not necessarily recur with all SSRIs, and tolerance may develop over time (36).

Drug-induced Parkinsonism, including dystonic reactions and akathisia, as well as worsening of motor disability in patients suffering from idiopathic Parkinson's disease, has been reported in older patients treated with SSRIs. In general, the positives of SSRI therapy far outweigh the potential for EPS, even in patients such as the elderly, who are at greater risk for movement disorder (37).

The tricyclic antidepressants (TCAs) are effective medications for major depressive disorders in the elderly and very elderly. Blood levels necessary to achieve a therapeutic effect for the very elderly are the same as for younger adults, although most older people are more sensitive to both the therapeutic and toxic effects of TCAs. While the TCAs are effective as antidepressants, altered pharmacokinetics and adverse effects may interfere with the usefulness of TCAs in treating very elderly patients with depression. Annoying side effects of TCAs, particularly constipation and dry mouth, can become severe problems in the elderly, leading to bowel obstruction and diminished ability to eat. Central nervous system anticholinergic side effects, which usually consist of decreased memory and attention, can progress to a delirious state with severe symptoms of cognitive impairment, nighttime confusion (sundowning), and delirium (16). Orthostatic hypotension, sedation, and cardiac toxic effects can also be particularly problematic for older persons (2). The most commonly used and studied TCAs have been nortriptyline and desipramine, because they have a more favorable side-effect spectrum than amitriptyline and imipramine (5).

In trials that directly compare SSRIs with TCAs, the SSRIs fluoxetine, sertraline, and paroxetine are roughly equivalent to TCAs in efficacy in the elderly, with 60–80% of patients responding to treatment (2). However, the SSRI sertraline was found to have a significant advantage over the TCA nortriptyline among patients 70 years old and over, with respect to time to achieve response and duration of remission (38). Interestingly, nortriptyline may be more effective than fluoxetine in elderly inpatients with severe depression and heart disease (2). However, unlike SSRIs, nortriptyline treatment has been associated with a significant increase in pulse rate in the elderly (38).

Other antidepressant drugs prescribed for elderly patients with depression include bupropion, venlafaxine, nefazodone and mirtazapine. Bupropion has no anticholinergic side effects. Venlafaxine resembles a TCA in pharmacologic properties but lacks anticholinergic effects. Nefazodone and mirtazapine are useful for bedtime sedation but may cause daytime drowsiness (16).

Monoamine oxidase inhibitors (MAOIs) are not frequently used to treat elderly patients because of concerns about side effects and drug interactions. They are well tolerated and effective in young-elderly patients (in their late 60s and 70s) with major depression, but they have not been adequately studied in the very old. The most frequent side effect of MAOIs is orthostatic hypotension, which in elderly patients may lead to falls. MAOIs require abstinence from tyramine-rich foods (mainly cheese and aged, pickled, or fermented meat or fish); otherwise, a hypertensive crisis may ensue. MAOIs have multiple drug-drug interactions. Concomitant administration of MAOIs with an SSRI may lead to a catastrophic serotonin syndrome (4).

With all antidepressants, clinicians usually "start low and go slow" (i.e., use low initial doses and increase the dose gradually) (16). Antidepressant drugs should be administered at adequate plasma levels or dosages and for a sufficient length of time. An adequate antidepressant trial for the elderly person may be longer than for the younger adult (4, 5), lasting up to 12 months.

Psychostimulants such as dextroamphetamine and methylphenidate have limited efficacy in treating geriatric major depression. However, psychostimulants appear to reduce apathy and anergy in medical patients. Psychostimulants have a rapid onset of action, minimal side effects, limited potential for tolerance, and a low risk for addiction (4, 34).

There is increasing recognition that a majority of major depressions are recurrent, particularly in the geriatric population; therefore, a central issue in treatment is the prevention of recurrence. Although there are relatively few clinical trials of maintenance treatment for elderly patients, continuation of antidepressants has been shown to confer significantly greater protection against recurrence than placebo. Although clinicians often reduce doses during the maintenance phase, preliminary evidence suggests that continuation of the dose and plasma level that was effective in the acute treatment phase offers increased protection against recurrence (5).

The recommendations for length of maintenance treatment are for at least 6 months of treatment beyond recovery for those with first onset in late life and for at least 12 months for those with a recurrent illness. Older patients with recurrent depression may need antidepressant treatment indefinitely to remain well (2). Some even suggest long-term treatment for all elderly patients with first-episode major depression (39). Long-term treatment should be of the same type and the same intensity as that which was successful in the initial, acute phase (2).

A number of augmenting techniques, e.g., techniques used to treat nonresponders or partial responders to antidepressants, have been used in the treatment of depression. Augmentation involves maintaining a therapeutic dose of an antidepressant and adding another agent. In younger adults SSRIs and TCAs have been shown to be augmented by lithium, triiodothyronine, buspirone, pindolol, and psychostimulants. However, most of these agents have not been studied in elderly populations. Lithium has been shown to augment tricyclic antidepressant response in elderly patients. Augmentation techniques are not well tolerated by a large number of geriatric patients (4).

Electroconvulsive Therapy

The evidence for short-term efficacy of electroconvulsive therapy (ECT) is strong (5). ECT is increasingly recognized as a useful treatment for severe or medication-resistant depression in older persons. In general, ECT is a low-risk procedure and is considered a safe, effective, and efficient treatment for depression. The efficiency of ECT does not diminish with age, and case reports attest to its safe use in patients as old as 102 (31).

Most patients have some degree of anterograde and retrograde amnesia during the treatment course, but most recover fully. There is no evidence that ECT causes structural brain disease, and in most cases there is no permanent objective cognitive deficit, with the exception of some loss of memory of events around the time of the ECT (31). ECT-induced delirium is transient and generally has a benign outcome. ECT is a safe treatment, with a mortality rate of 0.002–0.004%; 67% of deaths are due to cardiac complications immediately after or within a few hours of treatment. Dementing disorders are not a contraindication to ETC. Demented patients are more prone than nondemented patients to delirium and prolonged memory impairment. However, there is no evidence that ECT accelerates the course of dementing disorders (4). ECT has few absolute contraindications, and it can be lifesaving in appropriate circumstances (31).

Psychotherapy

Biological treatment may not resolve all of the problems associated with depression in the elderly. For example, significant and continuing life events, altered life roles, lack of social support, and chronic medical illnesses might well require psychosocial support and new coping skills (5). Older adults who suffer from depression are as likely to benefit from psychotherapeutic intervention as are younger adults (40, 41). Though psychotherapy combined with medication may be considered the "standard for appropriate care" for treating older adults with clinically significant depression (40, 41), psychotherapy has particular utility in older patients who cannot or will not tolerate medication (2, 41). Psychotherapy alone is also a powerful component of long-term treatment strategies and has been shown to provide substantial benefit in prolonging periods of good health free from depression (2, 41).

To date, cognitive-behavioral and interpersonal psychotherapies have the most empirical support, relative to other psychotherapies, as effective psychological interventions for late-life depression (2–5, 41). Psychodynamic psychotherapy also appears promising, but has been subjected to fewer empirical investigations (2, 4, 5, 41). Group interventions may be particularly appropriate for only a small proportion of depressed elders because many of these patients are uncomfortable with group settings (41). Family therapy for the elderly has received almost no research attention (3, 5, 41, 42), though treatment approaches that include selected family members may be particularly effective, given that most elderly depressed patients depend on family members for emotional support and for their day-to-day functioning (4). Caregivers of elderly patients, and especially of demented patients, often develop depression, which may also be effectively addressed by psychotherapeutic or family interventions (4).

Other Modalities of Treatment

Cross-sectional data from observational studies consistently demonstrate that a greater amount of occupational and leisure time physical activity is generally associated with reduced symptoms of depression (43).

Conclusion

Depression is a common public health problem among the elderly. Mental health and primary care providers should be familiar with the particularities of diagnosis and treatment for this population. Geriatric depression is eminently treatable. Recognition of this disorder is a vital step in the prevention of disability and mortality.

References

1. Bharucha AJ, Satlin A. Late-life suicide: a review. Harv Rev Psychiatry 1997; 5:55–65.
2. Lebowitz BD, Person JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. JAMA 1997; 278(14):1186–1190.
3. Anderson DN. Treating depression in old age: the reasons to be positive. Age Ageing 2001; 30:13–17.
4. Alexopoulos GS. Depression and other mood disorders. Clin Geriatr 2000; 8(11):69–82.
5. NIH Consensus Conference. NIH Consensus Development Panel on Depression in Late Life: diagnosis and treatment of depression in late life. JAMA 1992; 268(8):1018–1024.
6. Schulz R, Beach SR, Ives DG, et al. Association between depression and mortality in older adults. Arch Intern Med 2000; 160:1761–1768.

7. Angst J, Angst F, Stassen HH. Suicide risk in patients with major depressive disorder. J Clin Psychiatry 1999; 60(Suppl 2):57–62.
8. Pearson JL, Conwell Y. Suicide in late-life: challenges and opportunities for research. Int Psychogeriatr 1995; 7:131–136.
9. Pearson JL, Brown GK. Suicide prevention in late life: directions for science and practice. Clin Psychol Rev 2000; 20(6):685–705.
10. Peters KD, Kochanek KD, Murph SL. Deaths: Final data for 1996. National Vital Statistics Reports. Hyattesville (MD): National Center for Health Statistics; 1998 Nov 10. Vol. 47 #9.
11. Jacobs DG. A 52-year-old suicidal man. JAMA 2000; 283:2693-2699.
12. Lantz MS. Suicide in late life: identifying and managing at-risk older patients. Geriatrics 2001; 56(7):47–48.
13. Fawcett JA. Assessing and treating the patient at risk for suicide. Psychiatr Ann 1995; 23:244–255.
14. Conwell Y. Suicide in late life: a review and recommendations for prevention. Suicide Life Threat Behav 2001; 31(Spring Suppl):32–47.
15. American Psychiatric Association: Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): American Psychiatric Association; 1994.
16. Salzman C. Practical considerations for the treatment of depression in elderly and very elderly long-term care patients. J Clin Psychiatry 1999; 60(Suppl 20):30–33.
17. Nobler MS, Pelton GH, Sackeim HA. Cerebral blood flow and metabolism in late-life depression and dementia. J Geriatr Psychiatry Neurol 1999; 12:118–127.
18. Lai TJ, Payne ME, Byrum CE, et al. Reduction of orbital frontal cortex volume in geriatric depression. Biol Psychiatry 2000; 48:971–975.
19. MacFall JR, Payne ME, Provenzale JE, et al. Medial orbital frontal lesions in late-onset depression. Biol Psychiatry 2001; 49:803–806.
20. Baxter L, Schwartz JM, Phelps ME, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 1989; 46:243–250.
21. Sackeim HA, Prohovnik I, Moeller JR, et al. Regional cerebral blood flow in mood disorders: I. Comparison of major depressives and normal controls. Arch Gen Psychiatry 1990; 47:60–70.
22. Nobler MS, Mann JJ, Sackeim HA. Serotonin, cerebral blood flow, and cerebral metabolic rate in geriatric major depression and normal aging. Brain Res Brain Res Rev 1999; 30:250–263.
23. Rajkowska G, Miguel-Hidalgo JJ, Wei J, et al. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 1999; 45:1085–1098.
24. Rao R. Cerebrovascular disease and late life depression: an age old association revisited. Int J Geriatr Psychiatry 2000; 15:419–433.
25. Shih JC, Young H. The alteration of serotonin binding sites in aged human brain. Life Sci 1978; 23:1441–1448.
26. Wong DF, Wagner HN, Dannals RF, et al. Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science 1984; 226:1393–1396.
27. Bowen DM, Najlerahim A, Procter AW, et al. Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of later life. Proc Natl Acad Sci USA 1989; 86:9504–9508.
28. Brunello N, Riva M, Rovescalli A, et al. Age-related changes in rat serotonergic and adrenergic systems and in receptor responsiveness to subchronic desipramine treatment. Toxicology 1988; 63:150–155.
29. McEntee WJ, Crook TH. Serotonin, memory, and the aging brain. Psychopharmacology 1991; 103:143–149.
30. Marsh L. Neuropsychiatric aspects of Parkinson's disease. Psychosomatics 2000; 41(1):15–23.
31. Kelly KG, Zisselman M. Update on electroconvulsive therapy (ECT) in older adults. J Am Geriatr Soc 2000; 48(5):560–566.
32. Douyon R, Serby M, Klutchko B, et al. ECT and Parkinson's disease revisited: a "naturalistic" study. Am J Psychiatry 1989; 146(11):1451–1455.
33. Marin RS. Differential diagnosis of apathy and related disorders of diminished motivation. Psychiatric Ann 1997; 27(1):30–33.
34. Galynker II, Prikhojan A. Overlap of negative and depressive symptoms in non-schizophrenic patients: clinical implications. Directions in Psychiatry 1998;18:337–347.
35. Devane DL, Pollock BG. Pharmacokinetic considerations of antidepressant use in the elderly. J Clin Psychiatry 1999; 60(Suppl 20):38–44.
36. Kirby D, Ames D. Hyponatraemia and selective serotonin reuptake inhibitors in elderly patients. Int J Geriatr Psychiatry 2001; 16:484–493.
37. Pollock BG. Adverse reactions of antidepressants in elderly patients. J Clin Psychiatry 1999; 60(Suppl 20):4–8.
38. Bondareff W, Alpert M, Friedhoff A, et al. Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. Am J Psychiatry 2000; 157(5):729–736.
39. Flint AJ, Rifat SL. Recurrence of first-episode geriatric depression after discontinuation of maintenance antidepressants. Am J Psychiatry 1999; 156(6):943–945.
40. Niederehe G. Psychosocial treatments with depressed older adults: a research update. Am J Geriatr Psychiatry 1996; 4(Suppl 1):S66–S78.
41. Karel MJ, Hinrichsen G. Treatment of depression in late life: psychotherapeutic interventions. Clin Psychol Rev 2000; 20(6):707–729.
42. Benbow SM, Egan G, Mariott A. Using the family life cycle with later-life families. J Family Ther 1990; 12:321–240.
43. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. Med Sci Sports Exerc 2001; 33(6 Suppl):S587–S597.

Review of Dementia

Micheline Dugué, M.D., Judith Neugroschl, M.D.,
Margaret Sewell, Ph.D., and Deborah Marin, M.D.

Abstract

Elderly persons are at increased risk for developing dementia, and this risk increases with age. It is important to understand the following points: (a) how to diagnose dementia; (b) the etiology of the most common dementias (including Alzheimer's disease, ischemic vascular dementia, and diffuse Lewy body dementia); (c) some medical conditions which could contribute to symptoms of dementia; (d) the pathophysiology of Alzheimer's disease; and (e) management problems faced by caregivers for dementia patients. This review aims to educate clinicians to focus on caregivers' issues and the need for long-term planning.

Key Words: Dementia, elderly, Alzheimer's disease.

Introduction

Dementia is alarmingly prevalent in the elderly population, affecting 5% of people over the age of 65 and up to 50% of people over the age of 85 (1). It is essential to diagnose dementia accurately, so that appropriate interventions can be implemented. Currently, the underdiagnosis rate of dementia in primary care settings is as high as 75% (2), which may be related to the wide range of symptoms, from mild to severe, and the multiplicity of possible etiologies. Several causes of dementia (e.g., hypothyroidism or dementia syndrome of major depression) are totally reversible, although the vast majority of dementias (e.g., Alzheimer's disease and vascular dementia) are not reversible. With the advent of new treatments to slow progression of Alzheimer's disease (AD) and medications to decrease the risk of vascular events in vascular dementia, it is important to make an accurate diagnosis. Understanding the course of the dementing illnesses helps the clinician implement and monitor appropriate treatment for both the cognitive and behavioral aspects as well as undertake long-term planning with caregivers.

Diagnosing Dementia

Dementia vs. Mild Cognitive Impairment vs. Normal Aging

During an interview with a patient in whom memory impairment is suspected, it is important to review the clinical history and course of deterioration with both the patient and a knowledgeable informant (e.g., caregiver, family member) (3). Table 1 lists some helpful questions to ask. The history should include an assessment of:

- memory, language, orientation;
- activities of daily living;
- social, community, and intellectual functions;
- judgment;
- problem solving abilities;
- behavioral changes; and
- psychiatric symptoms.

Memory impairment is a necessary but not sufficient criterion for the diagnosis of demen-

---

From the Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Micheline Dugué, M.D., Instructor, Department of Psychiatry, Box 1230, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

This work is based on a presentation at the Geriatric Medicine Update and Board Review at the Mount Sinai School of Medicine, New York, NY on October 5–8, 2001.

tia; *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV TR) (4) criteria for dementia require a person to manifest at least one additional cognitive deficit (Table 1): aphasia (loss of language abilities), apraxia (inability to carry out specific tasks), agnosia (inability to recognize objects or persons) or impairment of executive functioning (abstract reasoning, flexibility in problem solving, adapting to changed situations). Moreover, these deficits must result in impairment of social or occupational functioning and represent a significant decline from a person's previous level of functioning (4).

To a very limited extent, some cognitive changes observed in AD occur in normal aging. Neuropsychological testing reliably distinguishes among changes associated with normal aging, mild cognitive impairment (MCI) and early AD. Age- and education-corrected norms are an essential component of teasing out the benign from the pathological.

In contrast to dementia, MCI is defined as impairment in memory only, with other cognitive functions spared. MCI is a syndrome that in a subgroup represents the earliest stages of AD (5). Approximately 15% of patients with MCI will progress to AD within a year, or up to 70% in 4–5 years (6, 7), compared to a 1–2% conversion rate in age-matched normal controls (8). Several multicenter drug trials are underway to ascertain whether treatment can slow or halt disease progression in this high-risk group (9).

The Differential Diagnosis of Dementia

For all dementias, an evaluation should include a comprehensive history, a physical examination (including neurological evaluation), laboratory tests, cognitive testing (Table 2), and neuroimaging (to rule out vascular lesions, tumors, subdural hematomas and normal pressure hydrocephalus).

TABLE 1
Questions That Help Elicit a History of Cognitive Impairment

	Questions to Ask Patient and Informant Separately
Memory	Does s/he have difficulty remembering recent conversations? Is s/he frequently repetitive? Is s/he aware of current events? Does s/he misplace or lose things? Does s/he forget to turn off the stove?
Language/ Aphasia	Dose s/he have difficulty finding the correct word? Is it sometimes difficult for others to understand him/her?
Orientation	Does s/he know where s/he is? The date/month/year? Does s/he forget upcoming holidays, birthdays, when to attend church, tax day, etc.?
Agnosia	Does s/he have difficulty recognizing people/places?
Activities of daily living	Does s/he have difficulty handling small sums of money? Does s/he have difficulty remembering short lists for shopping? Does s/he need assistance with eating, bathing, transfer in\and out of bed, walking, toileting, grooming or dressing?
Apraxia	Does s/he have difficulty using once familiar objects (e.g., toaster)? Does s/he have difficulty performing simple tasks at home? (e.g., making coffee, setting table, operating the TV, vacuum, etc.)
Problem-solving abilities	Does s/he have difficulty relating to newspapers or TV?
Executive functioning	Is s/he still able to manage finances/ the check book/taxes?
Social, community and intellectual function	Has s/he lost special skills, interests or hobbies (e.g., reading, sewing, cards, gardening) for reasons other than physical? Does s/he engage in socially inappropriate behavior?
Judgment	Does s/he show problems in judgment? (e.g., letting a stranger into the house)

TABLE 2
Dementia Work-up

Assessments	Rationale
*Labs: CBC, SMA, b12, folate, RPR, TSH	R/o correctable causes of dementia
*Imaging: ct without contrast or MRI	R/o infarcts, mass lesions, tumors, hydrocephalus
Neurologic exam	Correlate imaging findings with clinical exam
Neuropsychological testing	Formal description of cognitive impairments
*MMSE: screening test of cognitive function	

* Mandatory

TABLE 3
Other Possible Etiologies of Dementia

Neurologic Processes
Corticobasal degeneration
Normal pressure hydrocephalus
Traumatic brain injury
Huntington's disease
Parkinson's disease
Primary progressive aphasia
Brain tumor
Meningioma
Epilepsy
Progressive supranuclear palsy

Psychiatric Condition
Major affective disorder

Metabolic
HIV
Alcoholism
B12 or folate deficiency
Thyroid disorder

Hypotensive
Hypotoxic
CPR
Intubation
Hypoxic episode
Anemia

Neoplastic
Cancer

AD and vascular dementia are the most common illnesses in the differential diagnosis of a progressive, irreversible dementia. AD accounts for 55% of all dementias and vascular dementia for approximately 15% (Fig. 1). Other important etiologies for irreversible dementia include Lewy body dementia (10), frontotemporal dementia (11) and Parkinson's disease (12). Table 3 lists multiple etiologies for dementia, many of which refer to medical conditions and are reversible (13). It is important to include HIV infection and AIDS dementia, which are not reversible and are found in the elderly (14). The majority of these diagnoses account for 5 – 10% of dementias.

Contrary to prior thinking, AD is a diagnosis of inclusion, not exclusion (15, 16). In part, this conclusion is based on the fact that comprehensive evaluations are accurate 90% of the time, as confirmed by postmortem findings (17, 18). There has been a growing interest in diffuse Lewy body dementia (DLBD), which is thought to be a variant of AD. It is clinically defined as a dementia with fluctuating levels of impairment, recurrent visual hallucinations and Parkinsonian features (e.g., cogwheeling [tremor superimposed on rigidity], resting tremor and bradykinesia) (10, 19).

Following AD, vascular dementia is the most common dementia in the geriatric population in the U.S. and Western Europe. The criteria for diagnosing ischemic vascular dementia require evidence of at least one infarct (cortical or thalamic) that has a temporal relationship to the onset of dementia (20). Scattered white matter changes are very nonspecific findings that are strongly associated with age and hypertension. Severe confluent white matter changes are consistent with the diagnosis of Binswanger's disease (21), which is characterized by clinical features of dementia, incontinence and gait disturbance, similar to the triad of symptoms associated with normal pressure hydrocephalus.

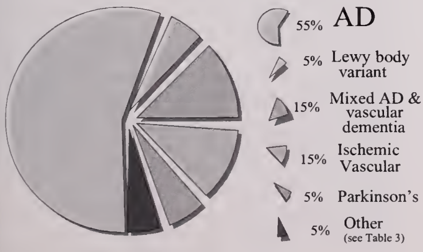

Fig. 1. Types of dementia in population 65+.

Mixed dementia should be diagnosed when: (a) there is a preexisting diagnosis of AD that is complicated by a stroke, with a subsequent decline in cognitive functioning; or (b) an AD course develops after the evidence of a single stroke that caused a cognitive decline. Mixed dementia is not an appropriate diagnosis if there only is a presence of cardiovascular risk factors or TIAs.

Pathophysiology of Alzheimer's Disease

The pathophysiology of AD includes the presence of neuritic plaques, tangles, neuronal loss, and neurochemical abnormalities. Extracellular amyloid plaques are formed from cleavage of the amyloid precursor protein (APP), a transmembrane protein, to an amyloidogenic end product. APP is cleaved by secretases to form either a 1-40 or 42 base pair amyloidogenic product (β Amyloid or Aβ), or a soluble product of another length. There are 3 secretases, α, β and γ, which cleave APP at different points (Fig. 2). The non-amyloidogenic α secretase cleaves APP near the plasma membrane, releasing soluble APP into circulation. β and γ secretase cleave APP to form toxic amyloid (i.e., beta-amyloid [Aβ]). The amyloidogenic fragment, Aβ 1-40, or the more amyloidogenic Aβ 1-42 aggregate to form insoluble β-pleated sheet fibrils, which form the nidus of plaque. Amyloid-plaque-related neurotoxicity leads to cell death by attracting inflammatory products. Some plaque is seen in normal aging brain (22), but it is the density of the plaques and not the number that correlates with cognitive impairment and disease severity in AD.

Neurofibrillary tangles are the result of abnormal tau protein production. Tau is used to stabilize microtubules. When tau is abnormally hyperphosphorylated, it forms paired helical filaments, which distort the architecture of microtubules into tangles. These neurofibrillary tangles impede the delivery of neurotransmitters along the axons and contribute to cell death (23).

The neuronal loss is attributed to the neurotoxicity of plaques and tangles and to the degeneration of the cholinergic system. The nucleus basalis of Meynert (nbM), the site of central production of acetylcholine (ACh), has projections throughout the cortex and particularly to the temporoparietal association cortex and to the entorhinal cortex and hippocampus. Thus, the neuronal loss affects both cortical and subcortical structures. Atrophy is demonstrated on imaging and autopsy. From early in the disease course, positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) scans may show reduced metabolism in the hippocampus and entorhinal cortex. As the disease progresses, there is decreased blood flow in the medial temporal structures and the temporoparietal association cortex (24). These special imaging techniques, however, are not routinely used to make the diagnosis of AD.

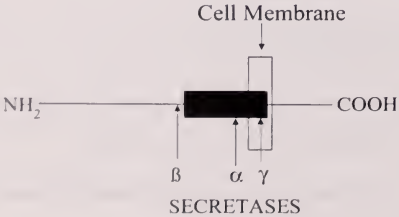

Fig. 2. Cleavage of amyloid precursor protein (APP) by secretases.

Several neurotransmitters (acetylcholine, norepinephrine, dopamine) and neuropeptides (somatostatin, corticotropin-releasing factor) are involved in AD. Deficits in acetylcholine, norepinephrine, corticotropin-releasing factor and somatostatin are found in moderate-to-advanced cases of AD (25). In cases of rapidly progressive AD and in patients younger than 65 years old, norepinephrine and serotonin deficits are found as well (26). The cholinergic deficit has been found to correlate with symptom severity in AD (27).

Since AD is genetically heterogenous and genetic transmission accounts for only a small percentage of cases, genetic testing is not routinely done for making the diagnosis. Genes on chromosomes 21, 19, 14, and 1 have been implicated in AD (see Table 4). A point mutation in the amyloid precursor protein gene, on chromosome 21, is associated with familial early onset AD. In addition, Down syndrome patients universally show AD pathology by age 30 (28). A dose effect of extra Aβ 1-42 burden is attributed to the additional chromosome.

The presenilin genes are transmitted as autosomal dominant with variable penetrance, and have been implicated in familial Alzheimer's disease. Presenilin 1 was mapped to chromosome 14, and presenilin 2 to chromosome 1. Presenilins are membrane-bound proteins of unclear function that may alter APP processing by promoting amyloidogenic Aβ. Presenilin 1 mutations account for approximately 50% of early onset familial AD. Presenilins may prove to be associated with the β and γ secretases (29). The β secretase, also called BACE (for beta-site APP-cleaving enzyme), has been cloned (30) and provides hope for the development of inhibitors to the production of amyloidogenic Aβ.

The apolipoprotein-epsilon (APOE) gene has been mapped to chromosome 19. ApoE is a cholesterol-carrying protein that may be involved in plaque metabolism. APOE genotype is related to plaque density and to increase in amyloid deposition in AD. There are 5 alleles of

TABLE 4
Chromosomal Defects Producing AD

Chromosome	Gene Defect	Age of Onset	AB Phenotype
21	Amyloid precursor protein	50s	Increased production of Aβ (1-42)
19	APOE ε4	60s	Increased density of Aβ plaques
14	Presenilin 1	40–50	Increased production of Aβ
1	Presenilin 2	50s	Increased production of Aβ

APOE, numbered ε1 to ε5. APOE ε1 and ε5 are rare alleles and have been implicated in hyperlipoproteinemia, but not in AD (31). APOE ε2 allele may confer protection from amyloid deposition (32, 33). The APOE ε3 allele, which does not seem to confer risk or benefit, is the most common allele, with 90% of the population inheriting one copy and 60% of Caucasians inheriting 2 copies (34). The APOE ε4 allele is associated with increased risk of AD. Thirty percent of the general population inherits one copy of APOE ε4 allele. On average, the frequency of APOE ε4 in AD ranges from 25–50%. Some APOE ε4 homozygotes have earlier onset, earlier mortality and a more severe course of AD (35–38). Because the absence of APOE ε4 does not preclude AD and its presence does not invariably lead to AD, APOE testing cannot be used to definitively predict development of AD and is not recommended as a diagnostic test for AD.

Management of Alzheimer's Disease Involves Pharmacologic and Psychosocial Interventions

Pharmacologic Management

There are four FDA-approved treatments for AD, all of which are all acetyl cholinesterase inhibitors (AChE-Is). In general, studies with cholinesterase inhibitors show improvement in cognitive function from baseline of 6–12 months (or 1.5–3 MMSE points [39]) for patients with mild-to-moderate AD (40). The response is usually most pronounced in moderate AD (41). AChE-Is differ in terms of target enzymes (acetyl choline or butyl cholinesterase), allosteric modulation of the nicotinic receptor, half-life, and side effect profile (Table 5). Tacrine hydrochloride (Cognex) is no longer used because it was associated with increased hepatic enzymes and/or gastrointestinal intolerance in more than 50% of patients. Nausea and vomiting may accompany the use of rivastigmine tartrate (Excelon), due to its actions on the butyl cholinesterase in the gastrointestinal tract. Donepezil hydrochloride (Aricept) may increase arousal and disturb sleep more than the other medications. Caution should be used in stopping an AChE-Is, as there is often a marked decline in cognition and function when discontinued (40). The newest FDA-approved treatment for AD in this class is galantamine hydrobromide (Reminyl), which inhibits acetyl cholinesterase and allosterically modulates the nicotinic receptor (42, 43). Galantamine has been studied in mixed Alzheimer's and vascular dementia, and was shown to be effective in maintaining cognition and behavior (44). There are no available studies comparing the effectiveness of one agent to the other. All agents show some improvement in cognition. The selection of a cholinesterase inhibitor should be based on ease of dose administration and tolerability.

Neuroprotective strategies are aimed at slowing disease progression in AD. The compounds studied to date include antioxidants, estrogen replacement therapy and anti-inflammatory agents. Use of antioxidants is based on their potential to reduce damage of excessive free radicals, as Aβ is known to cause oxidative stress in neurons (45). The most promising results were obtained in a clinical trial of patients with moderate-to-severe AD in which vitamin E 1000 IU bid was compared to 10 mg qd of selegiline (a monoamine oxidase type B [MAO-B] inhibitor, which has antioxidant and free-radical scavenging properties) and placebo. Treatment with vitamin E and/or selegiline slowed the progression of disease (46), but vitamin E is most widely recommended due to tolerability and lack of drug interactions.

Studies of estrogen replacement therapy looked promising in basic science, population studies and small clinical trials. In animal studies, estrogen was found to increase dendritic spines in hippocampal cells of ovarectomized rats (47) and to enhance learning (48). Large

TABLE 5
Acetylcholinesterase Inhibitors

	Donepezil	Rivastigmine	Galantamine
Features	Inhibits AChE	Inhibits BuChE and AChE	Allosteric modulation of nicotinic receptors Weak AChE inhibition
Dosing	5 – 10 mg qd	6 – 12 mg BID	12 – 16 mg BID
Medication-specific side effects*	Insomnia	Dizziness	Weight loss

*Side effects common to all: nausea, vomiting, diarrhea, myalgia, and anorexia.

population studies imply that estrogen may decrease risk of AD (49, 50). Patients to whom estrogen was administered with AChE-Is showed a more robust response to combination treatment in some small clinical trials (51, 52). These findings are in contrast to those of a multicenter, clinical trial of estrogen as a treatment for AD in which estrogen alone was equal to placebo for the treatment of cognitive disturbances in AD (53). Estrogen's effects may be most protective when used prior to the development of the disease.

Anti-inflammatory agents are used to target the central nervous system inflammatory response observed in AD. Population studies of patients with rheumatoid arthritis who are treated with NSAIDs show decreased risk of developing AD (54). Chronic use of NSAIDS (i.e., ibuprofen, naproxen) has been shown to delay the onset of AD in the general population (55). However, a multicenter trial of prednisone found no evidence of improvement nor slowed progress, as compared to placebo (56). An area of ongoing interest includes use of cyclooxygenase-2 (COX-2) inhibitors. COX-2 is upregulated *in vitro* in animal models and in the cortex of humans with AD (57).

New Directions for Treatment

New directions in treatment research look toward the protection of neurons. Degeneration of cholinergic cells from the excitatory neurotransmitter glutamate may be mitigated with memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist; this strategy may slow cognitive decline in AD (58, 59). Cholesterol-lowering statins, for example, may lower amyloid in the body, as cholesterol metabolism may be involved in the development of AD (60, 61). There is tremendous interest in anti-amyloid aggregative agents, which would also affect disease progression, and phase 1 trials are underway.

Plasma homocysteine has been evaluated as a risk factor for AD (62 – 64). Homocysteine may potentiate beta amyloid toxicity (65, 66), or vascular-related effects (67). Elevated homocysteine is an independent risk factor for AD (64). In fact, an increase in homocysteine of over 14 μmol/L almost doubles the risk of AD. Clinically, it will be important to see if interventions aimed at decreasing plasma homocysteine (i.e., treatment with folic acid, pyridoxine and cobalamin) affect AD risk.

Animal models of inhibitors of the secretases target the presenilin gene, given the role in memory deposition (68) and the BACE1 gene, for which a specific inhibitor has not been identified. Immunization with Aβ 1-42 in transgenic mouse models increased clearance and prevented deposition of plaque (68). Vaccination with amyloid resulted in brain inflammation in recent human clinical trials, which were suspended.

In summary, the current evidence-based regimen for AD patients includes a cholinesterase inhibitor and vitamin E. It is important to continue treatment with the AChE-Is for the reasons discussed above. Before the onset of the illness, anti-inflammatory agents and estrogen replacement therapy may decrease relative risk. Preliminary findings (69) support the use of estrogen with an AChE-Is in women with AD. The use of agents targeting other neurotransmitter systems, amyloid degradation, and amyloid aggregation are currently under investigation.

Psychosocial Management

The psychosocial management of AD requires that there be a dialogue between the clinician, patient, family, loved ones and caregivers. A session for diagnostic disclosure allows the clinician to review the results of the work-up and discuss treatment and prognosis. There is often pressure from families or caregiving friends to exclude the patient from this discussion. Interestingly, AD patients do not experience catastrophic reactions to the diagnosis (70). Understanding this fact and permitting patients to know their illness are of vital importance to family members. In deference to the patient and family concerned, as with any diagnostic disclosure, one should explore with the patient what he or she wishes to know. Discussion of the course of the illness and treatment options empowers the patient and their loved ones with options. Cognitive stimulation and memory enhancement programs have been found to be helpful (71).

Possible areas of concern to review with the family and loved ones include future planning and safety issues (e.g., driving, cooking, smoking, and firearms). Since AD patients will eventually lose the capacity to make financial, research and health care decisions, their inclusion in those discussions in the early-to-moderate stage of the illness is essential (72). Referral for legal assistance may be crucial for financial and estate planning, future needs and long-term care. It is also important to educate caregivers regarding changes in behavior, mood, agitation, and psychotic symptoms.

Caregivers of AD patients incur significant costs and burdens in the course of managing the illness. The spouse or eldest daughter often takes on the day-to-day caregiving of the patient. Paid home care is often used as a supplement to the unpaid care by family members (73). Studies of caregivers have found an increased risk for the emergence of psychopathology (e.g., substance abuse and depression) for the primary caregiver living with the AD patient in the community. Strategies for primary prevention of caregiver burnout include day centers for the patient, support groups, individual and family counseling, and paid care during the day or overnight. There is a wealth of information for patients and their loved ones, and physicians, available through the Alzheimer's Association (1-800-272-3900), http://www.alz.org, which provides pamphlets, books, videotapes and support groups.

Conclusion

Given the prevalence of dementia in the elderly and the availability of effective treatments, it is essential for the clinician to be able to diagnose and manage these illnesses. A careful assessment, including a complete history, laboratory evaluation and neuroimaging, should lead to an accurate diagnosis of the dementia subtype. Particularly in patients with mild symptoms, the diagnosis can be difficult and may require serial cognitive or neuropsychological testing. AD, the most common cause of dementia, is caused by neurotransmitter deficits and accumulation of amyloid plaques and neurofibrillary tangles. The FDA-approved pharmacotherapy for AD employs cholinesterase inhibitors, and there is evidence supporting the use of vitamin E to slow disease progression. Other neuroprotective strategies are currently being studied.

Ongoing dialogues with the patient and caregivers about the diagnosis and management of the illness are likely to improve expectations for the patient and the caregiver.

References

1. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. JAMA 1989; 262: 2551–2556.
2. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. Ann Intern Med 1995; 122(6):422–429.
3. Carr DB, Gray S, Baty J, Morris JC. The value of informant vs. individual's complaints of memory impairment in early dementia. Neurology 2000; 55:1724–1726.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV TR) Washington (DC): American Psychiatric Association; 2000.
5. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer's disease. Arch Neurol 2001; 58(3):397–405.
6. de Leon MJ, Convit A, DeSanti S, et al. Contribution of structural neuroimaging to the early diagnosis of Alzheimer's disease. Int Psychogeriatr 1997; 9 Suppl 1:183–190; discussion 247–252.
7. Bobinski M, de Leon MJ, Convit A, et al. MRI of entorhinal cortex in mild Alzheimer's disease. Lancet 1999; 353: 38–40.
8. Petersen RC, Smith GE, Waring SC, et al. Aging, memory and mild cognitive impairment. Int Psychogeriatr 1997; 9 Suppl 1:65–69.
9. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001; 58(12): 1985–1992.
10. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. Neurology 1996; 47:1113–1124.
11. Binetti G, Locascio JJ, Corkin S, et al. Differences between Pick disease and Alzheimer disease in clinical appearance and rate of cognitive decline. Arch Neurol 2000; 57(2):225–232.

12. Aarsland D. Cummings JL. Larsen JP. Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. Int J Geriatr Psychiatry 2001; 16(2):184 – 191.
13. Mayeux R. Foster NL. Rossor M. Whitehouse PJ. The clinical evaluation of patients with dementia. In: Whitehouse PJ. editor. Dementia. Contemporary neurology series. Vol. 40. Philadelphia (PA): F.A. Davis; 1993. pp. 92 – 129.
14. Meehan RA. Brush JA. An overview of AIDS dementia complex. Am J Alzheimers Dis Other Demen 2001; 16(4):225 – 229.
15. McKhann G. Drachman D. Folstein M. et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984; 34:939 – 944.
16. Small GW. Rabins PV. Barry PP. et al. Diagnosis and treatment of Alzheimer's disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry. The Alzheimer's Association and the American Geriatric Society. JAMA 1997; 278:1363 – 1371.
17. Blacker D. Albert MS. Bassett SS. et al. Reliability and validity of NINCDS-ADRDA criteria for Alzheimer's disease. The National Institute of Mental Health Genetics Initiative. Arch Neurol 1994; 51:1198 – 1204.
18. Hogervorst E. Barnetson L. Jobst KA. et al. Diagnosing dementia: interrater reliability assessment and accuracy of the NINCDS/ADRDA criteria versus CERAD histopathological criteria for Alzheimer's disease. Dement Geriatr Cogn Disord 2000; 11:107 – 113.
19. Minoshima S. Foster NL. Sima AA. et al. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann Neurol 2001; 50(3):358 – 365.
20. Chui HC. Victoroff JI. Margolin D. et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992; 42(3 Pt 1):473 – 480.
21. Caplan LR. Binswanger's disease — revisited. Neurology 1995; 45:626 – 633.
22. Price JL. Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999; 45:358 – 368.
23. Poorkaj P. Bird TD. Wijsman E. et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann Neurol 1998; 43:815 – 825.
24. Matsuda H. Cerebral blood flow and metabolic abnormalities in Alzheimer's disease. Ann Nucl Med 2001; 15(2):85 – 92.
25. Davis KL. Mohs RC. Marin DB. et al. Neuropeptide abnormalities in patients with early Alzheimer disease. Arch Gen Psychiatry 1999; 56(11):981 – 987.
26. Friedman JI. Adler DN. Davis KL. The role of norepinephrine in the pathophysiology of cognitive disorders: potential applications to the treatment of cognitive dysfunction in schizophrenia and Alzheimer's disease. Biol Psychiatry 1999; 46(9):1243 – 1252.
27. Davis KL. Mohs RC. Marin D. et al. Cholinergic markers in elderly patients with early signs of Alzheimer disease. JAMA 1999; 281(15):1401 – 1406.
28. Lemere CA. Blusztajn JK. Yamaguchi H. et al. Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: implications for initial events in amyloid plaque formation. Neurobiol Dis 1996; 3(1):16 – 32.
29. Lippa CF. Familial Alzheimer's disease: genetic influences on the disease process [review]. Int J Mol Med 1999; 4(5):529 – 536.
30. Vassar R, Bennett BD, Babu-Khan S, et al. Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 1999; 286(5440):735 – 741.
31. Ordovas JM, Litwack-Klein L, Wilson PW, et al. Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE1 and apoE5 isoforms. J Lipid Res 1987; 28(4):371 – 380.
32. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994; 7:180 – 184.
33. Locke PA, Conneally PM, Tanzi RE, et al. Apolipoprotein E4 allele and Alzheimer disease: examination of allelic association and effect on age at onset in both early- and late-onset cases. Genet Epidemiol 1995; 12:83 – 92.
34. Corder EH, Lannfelt L, Bogdanovic N, et al. The role of APOE polymorphisms in late-onset dementias. Cell Mol Life Sci 1998; 54:928 – 934.
35. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993; 43:1467 – 1472.
36. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 1993; 90:1977 – 1981.
37. Mayeux R, Stern Y, Ottman R, et al. The apolipoprotein 4 allele in patients with Alzheimer's disease. Ann Neurol 1993; 34:752 – 754.
38. Samuels SC, Silverman JM, Marin DB, et al. CSF beta-amyloid, cognition, and APOE genotype in Alzheimer's disease. Neurology 1999; 52(3):547 – 551.
39. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189 – 198.
40. Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomized, double-blind, placebo-controlled trial. The Donepezil Study Group. Dementia 1996; 7(6):293 – 303.
41. Kaufer D, Cummings JL, Christine D. Differential neuropsychiatric symptom responses to tacrine in Alzheimer's disease: relationship to dementia severity. J Neuropsychiatry Clin Neurosci 1998; 10(1):55 – 63.
42. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000; 54(12):2261 – 2268.
43. Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 2000; 54(12):2269 – 2276.
44. Erkinjuntti T, Kurz A, Gauthier S, et al. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002; 359(9314):1283 – 1290.
45. Behl C, Davis JB, Lesley R, Schubert D. Hydrogen peroxide mediates amyloid beta protein toxicity. Cell 1994; 77(6):817 – 827.
46. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997; 336(17):1216 – 1222.
47. Frankfurt M, Gould E, Woolley CS, McEwen BS. Gonadal steroids modify dendritic spine density in ventromedial hypothalamic neurons: a Golgi study in the adult rat. Neuroendocrinology 1990; 51(5):530 – 535.

48. Luine VN, Richards ST, Wu VY, Beck KD. Estradiol enhances learning and memory in a spatial memory task and effects levels of monoaminergic neurotransmitters. Horm Behav 1998; 34(2):149–162.
49. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med 1996; 156(19):2213–2217.
50. Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996; 348(9025):429–432.
51. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. Neurology 1996; 46(6):1580–1584.
52. Ohkura T, Isse K, Akazawa K, et al. Long-term estrogen replacement therapy in female patients with dementia of the Alzheimer type: 7 case reports. Dementia 1995; 6(2):99–107.
53. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer's disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA 2000; 283(8):1007–1015.
54. McGeer PL, McGeer E, Rogers J, Sibley J. Anti-inflammatory drugs and Alzheimer's disease [letter]. Lancet 1990, 335(8696):1037.
55. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997; 48(3):626–632.
56. Aisen PS, Davis KL, Berg JD, et al. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. Neurology 2000; 54(3):588–593.
57. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology 1996; 47:425–432.
58. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999; 14(2):135–146.
59. Wenk GL, Quack G, Moebius HJ, Danysz W. No interaction of memantine with acetylcholinesterase inhibitors approved for clinical use. Life Sci 2000; 66(12):1079–183.
60. Simons M, Keller P, De Strooper B, et al. Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc Natl Acad Sci U S A 1998; 95(11):6460–6464.
61. Buxbaum JD, Cullen El, Friedhoff LT. Pharmacological concentrations of the HMG-CoA reductase inhibitor lovastatin decrease the formation of the Alzheimer beta-amyloid peptide in vitro and in patients. Front Biosci 2002; 7:a50–a59.
62. Joosten E, Lesaffre E, Riezler R, et al. Is metabolic evidence for vitamin B-12 and folate deficiency more frequent in elderly patients with Alzheimer's disease? J Gerontol A Biol Sci Med Sci 1997; 52:M76–M79.
63. Clarke R, Smith AD, Jobst KA, et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998; 55:1449–1455.
64. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002; 346:476–483.
65. Ho Pl, Collins SC, Dhitavat S, et al. Homocysteine potentiates beta-amyloid neurotoxicity: role of oxidative stress. J Neurochem 2001; 78:249–253.
66. White AR, Huang X, Jobling MF, et al. Homocysteine potentiates copper- and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's-type neurodegenerative pathways. J Neurochem 2001; 76:1509–1520.
67. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998; 338:1042–1050.
68. Feng R, Rampon C, Tang YP, et al. Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. Neuron 2001; 32(5):911–926.
69. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. Neurology 1996; 46(6):1580–1584.
70. Tiberti C, Sabe L, Kuzis G, et al. Prevalence and correlates of the catastrophic reaction in Alzheimer's disease. Neurology 1998; 50(2):546–548.
71. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002; 287(6):742–748.
72. Marin DB, Green CR, Schmeidler J, et al. Noncognitive disturbances in Alzheimer's disease: frequency, longitudinal course, and relationship to cognitive symptoms. J Am Geriatr Soc 1997; 45(11):1331–1338.
73. Marin DB, Dugue M, Schmeidler J, et al. The Caregiver Activity Survey (CAS): longitudinal validation of an instrument that measures time spent caregiving for individuals with Alzheimer's disease. Int J Geriatr Psychiatry 2000; 15(8):680–686.

Urinary Incontinence in the Geriatric Population

Adam P. Klausner, M.D.[1], and Jonathan M. Vapnek, M.D.[2]

Abstract

Background: Urinary incontinence is a widespread, yet potentially treatable, problem in the geriatric population.
Methods: We reviewed the geriatric and urologic literature to provide an update on the definition, diagnosis, and treatment of geriatric urinary incontinence.
Results: Urinary incontinence affects 15–30% of elderly individuals in the community and 50% of those living in nursing homes. Both age and gender affect bladder function, and incontinence affects females and males in a ratio of 2:1. Incontinence can be classified as urge, stress, overflow, functional, or mixed. There are many reversible causes of incontinence, and a thorough history and physical examination, including a complete voiding history and a tailored neuro-urologic examination, are required for accurate diagnosis. Treatment options include behavioral modification, medical therapy with anticholinergics or hormone replacement, and surgical intervention.
Conclusions: Urinary incontinence, due to many causes, is a widespread problem among the elderly. Yet many of these causes are reversible with appropriate treatment, often by the primary care provider. Some patients may require urologic referral for sophisticated urodynamic studies and possible surgical intervention, in select cases.
Key Words: Incontinence, voiding dysfunction, geriatric.

Introduction

INCONTINENCE is a widespread, yet potentially treatable, condition in the geriatric population. It affects 15–30% of elderly individuals living in the community and is even more prevalent in nursing homes, where approximately 50% are affected by incontinence (1). It is frequently underreported and undertreated because of the mistaken belief that incontinence is part of the normal aging process. The true incidence is probably much higher. The economic and social costs of incontinence are staggering. Annually, more than $3 billion is spent managing incontinence in nursing homes alone (2). Furthermore, there are tremendous personal and social costs, including effects on the morale of patients and their caregivers, social isolation, immobility, and unnecessary institutionalization. Some problems may arise because incontinent individuals adapt their behaviors to avoid public embarrassment due to urine leakage.

Effects of Age and Gender on Bladder Function

Bladder function is altered in many ways by the aging process. More than half of normal elderly individuals experience the symptom of nocturia. Overall bladder capacity is reduced, as is the urethral closure pressure (a measure of urinary sphincteric function). Post-void residual urine volumes are elevated, and patients tend to produce larger volumes of urine as a result of a reduction in renal concentrating ability. Uninhibited detrusor contractions may be seen in 10% of women and 30% of men (3). Aging can lead to slowed reaction times and limited mobility, which may affect a patient's ability to get to bathroom facilities in a timely manner. In addition, benign prostatic hyperplasia (BPH), with resultant bladder outlet obstruction, becomes more prevalent in elderly men (4).

---

[1] Chief Resident and [2] Clinical Associate Professor and Director of Voiding Dysfunction, Department of Urology, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Jonathan M. Vapnek, M.D., Department of Urology, Box 1272, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

This work is based on a presentation at the Geriatric Medicine Update and Board Review at the Mount Sinai School of Medicine, New York, NY on October 5–8, 2001.

Older women have an even higher predisposition to develop urinary incontinence than older men, in a ratio of 2:1. Histologically, hypertrophic changes in bladder smooth muscle, collagen, and elastic tissue occur more frequently in elderly women. Furthermore, there may be degeneration and fibrosis of the bladder wall and decreased bladder capacity, as well as diminished muscle tone in the bladder, internal and external sphincters, and pelvic floor musculature. There is also a reduction in bladder contractility. The exact reasons for these gender-related changes are not entirely known. However, contributory factors include: a history of childbearing, gynecologic procedures, hormonal changes occurring after the onset of menopause, and obesity.

Classification of Urinary Incontinence

As defined below, incontinence may be classified as urge, stress, overflow, functional, or mixed:

- **Urge incontinence** is defined as leakage of urine associated with a sudden, strong desire to void. This is often associated with bladder overactivity on cystometric analysis, but it is not specific for this condition. Urodynamically documented bladder overactivity has traditionally been subdivided into two categories, based on the presence or absence of associated neurologic conditions. Detrusor instability was the term used to describe bladder overactivity occurring in the absence of neurologic conditions, while detrusor hyperreflexia was used to describe bladder overactivity associated with known neurologic conditions. The International Continence Society has recently changed the terminology, and the preferred terms are idiopathic detrusor overactivity and neurogenic detrusor activity (Figure) (5). Idiopathic detrusor overactivity may be seen with bladder irritation from urinary tract infection (UTI), vaginitis, fecal impaction, stones, and other local causes, while neurogenic detrusor overactivity is seen in upper motor neuron lesions, stroke, multiple sclerosis, Parkinson's disease and spinal cord injury.

- **Stress incontinence** is defined as leakage of urine that occurs with increases in intra-abdominal pressure from coughing, sneezing, laughing, straining, or exercising. It is associated with pelvic floor muscle laxity, neuropathy, and prior urologic surgery. Risk factors include multiple childbirths and traumatic deliveries (Table 1).

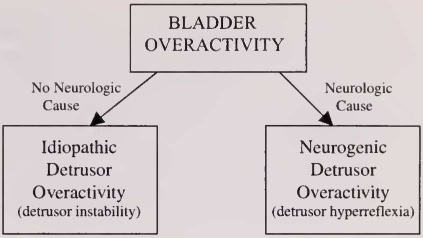
BLADDER OVERACTIVITY
No Neurologic Cause
Neurologic Cause
Idiopathic Detrusor Overactivity (detrusor instability)
Neurogenic Detrusor Overactivity (detrusor hyperreflexia)

Fig. Subclassification of bladder overactivity.

- **Overflow incontinence** is defined as leakage of urine associated with an overfilled bladder. This has also been termed "paradoxical incontinence," because symptoms of urgency and frequency occur despite the

TABLE 1

Work-up of Female Stress Urinary Incontinence

History	Number of childbirths Delivery type Prior pelvic surgery
Physical Examination	Vaginal speculum examination –atrophic vaginitis –urethral prolapse –cystocele –uterine prolapse –rectocele –enterocele
Specialized Tests	Marshall test Q-Tip test (positive if >30 degrees) Urodynamics
Treatments	Behavioral modification –Kegel exercises –biofeedback Medical therapy –hormones (atrophic vaginitis) –alpha-agonists Surgical treatments –retropubic/vaginal suspensions –pubovaginal slings –artificial sphincters –submucosal bulking agents

presence of a full bladder. The causes include outlet obstruction, poor detrusor contractility, and impaired sensation of fullness.

- **Functional incontinence** is defined as leakage of urine that occurs in the setting of normal bladder and urethral function in an individual who has poor mobility or mental confusion. This type is quite common in elderly, debilitated, and institutionalized patients.

- **Mixed incontinence** is defined as leakage of urine attributed to multiple factors, as defined above.

Recently, the term "overactive bladder" was added to the classification scheme. This entity, which may or may not be associated with urge incontinence, is a condition in which an individual voids at least eight times during the day and/or twice at night. The term, however, is very nonspecific and gives no insight into the underlying pathophysiology. It may imply detrusor overactivity, or it may simply reflect patient habit. A patient with genuine stress urinary incontinence, for example, may void frequently in order to reduce the probability of incontinence episodes. Classifying this patient as having an overactive bladder oversimplifies the problem and could potentially delay both proper diagnosis and treatment. The term "overactive bladder" should therefore be used with caution by physicians and patients alike.

Finally, a common problem seen almost exclusively in the elderly is detrusor hyperactivity with impaired contractility (DHIC) (6). This condition is perhaps the most common cause of incontinence in the frail elderly (7) and can be very difficult to diagnose and treat. Diagnostically, this disorder may mimic either stress or urge incontinence. Treatment with anticholinergic agents may be difficult because of the risk of precipitating urinary retention.

Reversible Causes of Geriatric Incontinence

In the elderly population, there are many non-urologic conditions which predispose individuals to urinary incontinence. Treatable causes may best be remembered by the acronym DIAPPERS and are listed in Table 2.

TABLE 2

*Reversible Causes of Geriatric Incontinence: "DIAPPERS."**

D	**D**elirium /Dementia
I	**I**nfections (urine, vagina)
A	**A**trophic vaginitis
P	**P**sychological causes (especially depression)
P	**P**harmaceutical agents
E	**E**ndocrine conditions (diabetes)
R	**R**estricted mobility
S	**S**tool impaction

*Modified with permission from Resnick NM, Yalla SV. Geriatric incontinence and voiding dysfunction. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's urology. 7th ed. Philadelphia (PA): W.B. Saunders Co.; 1998. p. 1045 (7).

History and Physical Examination

In order to make the correct diagnosis, a thorough history and physical examination is imperative for patients in this age group. Comorbid medical problems may contribute to incontinence and should be carefully noted. Conditions such as diabetes mellitus, Parkinson's disease and cerebrovascular accident (CVA) commonly affect voiding function in a variety of ways. A history of all active pharmacotherapy is also important, since medications such as diuretics, anticholinergics and narcotic analgesics can affect voiding function.

A voiding history must be obtained, and patients or caretakers should be questioned about obstructive and irritative symptoms. Obstructive symptoms include straining, decreased force of stream, intermittent flow, and hesitancy. Irritative symptoms include urgency, frequency, and urge incontinence. A history of prior surgery, especially pelvic or spinal surgery, is important, as disruption of nerve pathways supplying the bladder and urethral sphincter can sometimes occur during these types of procedures. A history of prior trauma is also important. A voiding diary is a means for patients to provide objective data, by documenting the number of bathroom visits, the number of protective pads used, and even the volume of urine per void (Table 3). This may be a difficult task for some patients to perform, especially those with cognitive impairment. However, caregivers can be extremely helpful in providing this valuable information. From these sources, data can be collected at baseline and during treatment, to document an objective response to treatment.

A tailored physical examination is also required when evaluating the geriatric patient with incontinence. The abdomen should be inspected for scars, and palpated for masses,

TABLE 3

Sample Voiding/Incontinence Record

Date	Time	Voids Wet/Dry	Volume	Pads	Severity of Leakage (mild, moderate, severe)	Comment
11/1	7:45am	Wet	Approx 150 cc	3	moderate	Running for the bus
	11:20am	Dry	100 cc	*	*	*
	2:30pm	Dry	100 cc	*	*	*
	4:15pm	Wet	Approx 200 cc	*	mild	Coughing
	7:00pm	Wet	Approx 100 cc	*	mild	Coughing
	11:15pm	Dry	300 cc	*	*	*
11/2	7:30am	Dry	400 cc	2	*	1st am void
	11:15am	Dry	200 cc	*	*	(no coffee today)
	4:10pm	Wet	Approx 150 cc	*	moderate	Laughing
	7:00pm	Wet	Approx 100 cc	*	mild	Sneezing
	11:30pm	Dry	300 cc	*	*	*

* = not recorded

bladder distension and costovertebral angle tenderness. In men, a rectal examination gives information about the size and consistency of the prostate. A neuro-urologic examination should be performed, in which perianal sensation (including the sacral S2-4 dermatomes), anal sphincter tone and voluntary pelvic floor contractions are tested (Table 4). Furthermore, the bulbocavernosus reflex should be elicited. In this test, the examiner pinches the glans penis or clitoris (or pulls gently on an indwelling urethral catheter) while the index finger of the opposite hand is inserted in the rectum. A contraction of the anal sphincter demonstrates that the bulbocavernosus reflex is intact. While this reflex may be absent in more than 30% of normal individuals, its presence rules out significant sacral neuropathy and proves that the sacral reflex pathways are intact.

In women, a vaginal examination can detect mucosal friability, petechiae, telangiectasia, and vaginal erosions, which are the hallmarks of atrophic vaginitis. A pelvic bimanual examination can also identify pelvic floor descent or prolapse of pelvic organs, including urethrocele, cystocele, enterocele, uterine, vaginal, and rectal prolapse. Simple objective tests for stress urinary incontinence can also be performed. To document hypermobility of the bladder neck and urethra, the posterior blade of a vaginal speculum is inserted and the posterior vaginal wall retracted. By asking the patient to bear down or cough, the degree of support anteriorly can be assessed. If leakage of urine through the urethral meatus is observed, the diagnosis of stress incontinence is confirmed.

TABLE 4

Tailored Neuro-urologic Examination

S2–S4 dermatomes — Pinprick sensation
Lower extremity reflexes
Bulbocavernosus reflex test
Anal sphincter tone
Voluntary pelvic contractions

When anterior vaginal wall hypermobility and stress incontinence are documented, a Marshall test can be performed. A clamp with a folded gauze pad is used, and the base of the bladder and urethra are supported and lifted retropubically, making sure not to actually occlude the bladder outlet. A positive Marshall test occurs when previously demonstrated incontinence is eliminated after this pressure is applied. This indicates that bladder neck suspension procedures may potentially cure the incontinence. Likewise, the Q-Tip test is a simple measure of urethral hypermobility. In this test, a well-lubricated, sterile, cotton-tipped applicator is inserted into the urethra with the bladder full. The patient is then asked to perform a Valsalva's maneuver, and the change in the angle of the applicator is noted. An angle change of greater than 30 degrees is suggestive of urethral hypermobility.

Laboratory Work-up

Laboratory investigations are sometimes necessary to aid in the diagnostic process. For all patients, a urinalysis and culture as well as a serum blood urea nitrogen and creatinine level should be obtained. A finding of microscopic hematuria (usually defined as more than five red blood cells per high-powered microscopic field in the spun urinary sediment) warrants further investigation, including imaging studies of the urinary tract, urinary cytology, and cystoscopic examination of the bladder. In this way, the presence of potentially treatable entities such as urinary calculi, renal masses, urothelial malignancies, and carcinoma-*in-situ* of the bladder can be identified.

A large number of elderly patients, especially those with indwelling catheters or external collecting devices, have pyuria (usually defined more than 10 white blood cells per high-power microscopic field in the spun urinary sediment) or bacteriuria (8). In general, however, asymptomatic pyuria or bacteriuria in these patients should not be treated. In this setting, treatment selects for more pathogenic strains of bacteria and bacterial resistance. Furthermore, long-term cure rates are no different than for those receiving placebo therapy, due to common re-infections and the occurrence of spontaneous cures (9). The exception to this rule is the presence of asymptomatic infections with proteus species. Because of its urease activity, this bacterium is associated with the formation of infection or struvite stones. Therefore, proteus infection, symptomatic or asymptomatic, should always be treated. Also, the physician should be aware that urinary tract infections may not present in the typical manner in the elderly population. Lethargy and confusion, for example, may replace the more common presenting symptoms of fever and dysuria. A high index of suspicion is therefore required.

Radiologic Work-up

Imaging studies may be necessary in the work-up of certain patients with incontinence. Renal sonography is useful for men with post-void residual urine volumes greater than 100 mL, to rule out hydronephrosis or other upper tract lesions. Likewise, for any patient with associated hematuria (either microscopic or gross), evaluation of the status of the upper urinary tract is mandatory. This evaluation would include sonography, intravenous urography or occasionally computed tomography or magnetic resonance imaging. A cystogram can provide information regarding the lining of the bladder or the presence of stones, tumors, diverticulae, or fistulae. A voiding cystourethrogram (VCUG) is used to identify urinary reflux and to evaluate for urethral lesions. These imaging studies should only be used in a select subset of patients.

Urodynamics

Formal urodynamic testing is not mandatory for all incontinent individuals, but it is useful to help clarify the diagnosis for patients with complicated histories. Formal urodynamics is also indicated for patients for whom empiric therapy is unacceptable or has failed, or for whom surgical intervention is planned (10). An example is an elderly male patient with Parkinson's disease in whom bladder outlet obstruction from BPH as well as neurologic voiding dysfunction may contribute to his overall clinical picture.

Cystoscopy

The need for a cystoscopic evaluation is by no means universal and should be tailored to the individual patient. In selected cases, cystoscopy may identify the presence of tumor and bladder trabeculations, and evaluate urethral integrity. Certain types of fistulae such as colovesical fistulae, which can occur as a complication of sigmoid diverticulitis, or vesicovaginal fistulae, which may occur after complicated gynecologic surgeries or after radiotherapy for cervical carcinoma, can often be identified through the cystoscope. In addition, cystoscopy provides valuable information about the size and configuration of the prostate and is useful in men with BPH who are candidates for transurethral resection of the prostate.

Treatment of Incontinence in the Elderly

Behavioral Approaches

Behavioral therapy has been shown to be an effective tool in managing several types of incontinence experienced by the elderly. Techniques include bladder training, pelvic floor muscle exercises, and biofeedback. "Bladder training" refers to a regimen of gradually increasing the intervals between voiding episodes. "Pelvic floor rehabilitation," also called Kegel maneuvers or Kegel exercises, refers to a regimen of exercises designed to strengthen the urethral sphincter and levator muscles of the pelvic floor. Biofeedback combines Kegel maneuvers with computer or other technologies which are used to translate physiological information into visual or audible signals. All of these techniques have been shown to reduce the degree of urinary incontinence of both the urge and stress varieties.

In the geriatric patient population in nursing homes and similar facilities, simple behavioral interventions have been quite effective in the treatment of incontinence. Hu et al. (11) performed a study in which demented and dependent nursing home patients were checked hourly and prompted to void. With this regimen, there was a 26% overall reduction in incontinence, and 38% of the patients improved by more than 50%. While many studies have confirmed the effectiveness of prompted voiding techniques in elderly nursing home patients, the available data indicates that these effects are primarily seen in the short term (12).

Medical Approaches

Drug therapy for geriatric incontinence includes anticholinergics, hormones, alpha-antagonists, and several miscellaneous agents. Practitioners sometimes avoid use of these medications for the elderly for fear of heightened side effects. This question was addressed in a study examining the effects of oxybutynin pharmacokinetics in the elderly population (13). In this study, serum oxybutynin levels were tested in 21 elderly patients being treated with oxybutynin at 2.5 mg or 5.0 mg three times daily, and compared with a control population of healthy young men treated similarly. The results demonstrated that there were no differences in mean peak plasma levels between the two age groups. Overall, two-thirds of the patients experienced minor side effects, usually dry mouth. The authors therefore concluded that this anticholinergic medication in normal doses is safe for use by the elderly.

Newer anticholinergic medications with improved side-effect profiles and less frequent dosing schedules have recently become available. An example is tolterodine tartrate (Detrol®), available at 1 mg and 2 mg and administered twice daily. Long-acting forms of tolterodine tartrate (Detrol LA®, available as a once-daily dose of 4 mg) and oxybutynin (Ditropan XL®, available as a once-daily dose of 5–15 mg) are now on the market and approved for use. These agents are generally well tolerated and seem to be associated with improved patient compliance.

Oral and topical estrogen therapy have been mainstays in the treatment of urgency and frequency caused by atrophic vaginitis and urethritis. Preparations include low-dose, unconjugated oral estrogens or topical, intravaginal, conjugated estrogen cream. A course of treatment should be administered for one to two months. The estradiol vaginal ring (Estring®) is a 90-day, sustained-release form of estradiol consisting of a silicone ring that is impregnated with estradiol. Women with an intact uterus should have cyclic progesterone therapy added to their hormone regimens. Because estrogen therapy is a known risk factor for the development of endometrial cancer, the risks and benefits of therapy should be discussed with all patients, and patients with a history of breast cancer should not receive this treatment. There have been many articles on the use of both oral and topical estrogen supplementation in the postmenopausal patient. The rates of cure or improvement ranges from 0–65%. Many other studies have been carried out under less than ideal circumstances. In a meta-analysis, it was concluded that estrogen did provide substantial subjective improvement (14).

However, for stress incontinence, the role of hormone therapy is less well established. Some studies show increases in urethral closure pressure with use of estrogen therapy (15). In addition, the use of combination therapy with alpha-agonists and estrogen therapy has had some success, but the results appear to be similar to those for patients treated with behavioral therapy (16). Furthermore, estrogen may be useful in the preoperative period, to maximize the benefits of surgical therapy.

Alpha-blocker therapy is a mainstay of treatment for BPH in elderly men. Smooth muscle of the prostate is rich in alpha receptors (17) and alpha blockade provides symptom relief for a majority of patients (18). Notable side effects include dizziness, hypotension, and sexual dysfunction. Patients are therefore advised to take these medications (including terazosin and doxazosin) at bedtime, and gradual dose escalation is often required. Recently, a newer prostate-selective alpha-blocking agent, tamsulosin, has become available. The advantage of this agent is that hypotension does not occur. Morning dosing is therefore possible and dose escalation is not necessary. In men with large prostates (over than 40 grams), 5-alpha-reductase inhibition therapy with finasteride can be prescribed. This agent causes a reduction in prostate volume, but takes up to three months to achieve maximal effects (19).

Surgical Approaches

Surgical therapy is available for correction of incontinence for appropriate patients. Bladder neck suspension and sling procedures are used for treatment of stress urinary incontinence in female patients. Urethral hypermobility is corrected during common retropubic bladder neck suspensions such as the Marshall-Marchetti-Krantz procedure, in which the anterior paravaginal fascia is attached to the posterior pubis, and the Burch colposuspension, in which the anterior paravaginal fascia is attached to Cooper's ligament. Transvaginal needle suspension procedures such as the Raz and Stamey procedures produce similar results. However, these procedures do not treat intrinsic sphincter deficiency, which is a common cause for primary post-operative failures. Pubovaginal sling procedures, in which a piece of autologous fascia, donor fascia, or synthetic material is placed under the urethra and secured, have been developed to address the problem of intrinsic sphincter deficiency. The creation of a "backboard" under the urethra and bladder neck treats both hypermobility and sphincter deficiency, and explains why this procedure has grown in popularity among practicing urologists.

Artificial urinary sphincters are sometimes used to correct incontinence in male patients who have post-prostatectomy incontinence or neurologic causes of intrinsic sphincter deficiency. Some medical centers implant artificial sphincters occasionally in women in order to correct severe forms of intrinsic sphincter deficiency. BPH can be effectively treated with transurethral resection of the prostate or simple prostatectomy in patients who fail medical therapy.

Miscellaneous Treatments

Newer treatments for incontinence include electrical stimulation of sacral nerve roots via an internal or external device or injection of bulking agents such as collagen around the urinary sphincter. For patients not helped by medical therapy for overactive bladder and/or urge incontinence, sacral nerve stimulation (Interstim®, Medtronic, Minneapolis, MN) is a relatively new option that is available. In this technique, one of the sacral nerve roots is stimulated percutaneously using an insulated needle, in the outpatient setting. A thin stainless steel wire is left in place, and the patient wears a small stimulator for 3 – 7 days. If a greater than 50% reduction in symptoms is achieved during this test stimulation, the patient becomes a candidate for placement of a permanent stimulator. In this surgical procedure, a permanent electrode is inserted into the sacral foramen and is secured in place along with an implantable pulse generator which can provide years of stimulation. This technique has been quite successful in some of the most difficult cases (20). A good response to short-term percutaneous stimulation predicts a successful permanent implant, and long-term data demonstrates durable results (21).

Transurethral injections of collagen and other bulking agents such as Durasphere® (Carbon Medical Technologies, Inc., St. Paul, MN) (silicone-coated carbon particles) have been used for women with intrinsic sphincter deficiency in whom poor urethral coaptation is the most relevant etiologic factor. Placement of the bulking agents in a submucosal plane improves coaptation of the urethral mucosa, allowing for an improved "seal effect." The principal advantage of these agents is that the procedure can be done on an outpatient basis using local anesthesia or light sedation, and it can be repeated if necessary. Although the short-term results with injectables are quite promising, durable long-term results and prospective comparison to formal anti-incontinence surgery are not available (22). However, the lack of morbidity and the ability to repeat the procedure make it especially attractive for the geriatric population.

Indications for Urological Referral

Incontinence is a complicated and often debilitating condition in the geriatric population. Many, if not most, patients can be easily treated by primary care physicians and geriatricians. However, some challenging clinical situations warrant referral to a urologist. Referral is indicated for patients with high post-void residual volume (>200 cc), severely limited bladder capacity (<100 cc), recent pelvic surgery or irradiation, frequent UTIs, hematuria, and marked pelvic prolapse. In addition, men and women with stress urinary incontinence who are candidates for surgical correction should be referred.

Conclusions

Incontinence is a widespread condition in the elderly population. However, many treatable causes can be identified with a thorough history and physical examination, which include a voiding history and a tailored neurourologic examination. Treatment options for geriatric incontinence include behavior modification, medical therapy, and surgical intervention. Complicated cases may require urologic referral for sophisticated urodynamic evaluations, cystoscopy, or surgical therapy.

References

1. Brandeis GH, Baumann MM, Hossain M, et al. The prevalence of potentially remediable urinary incontinence in frail older people: a study using the Minimum Data Set. J Am Geriatr Soc 1997; 45:179–184.
2. Hu TW. Impact of urinary incontinence on health-care costs. J Am Geriatr Soc 1990; 38:292–295.
3. Hunskaar S, Arnold EP, Burgio K, et al. Epidemiology and natural history of urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunc 2000; 11:301–319.
4. Resnick NM, Elbadawi A, Yalla, SV. Age and the lower urinary tract: what is normal? Neurourol Urodyn 1995; 14:577–579.
5. Abrams P, Cardozo L, Fall M, et al. The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21:167–178.
6. Griffiths DJ, McCracken PN, Harrison GM, et al. Urge incontinence and impaired detrusor contractility in the elderly. Neurourol Urodyn 2002; 21:126–131.
7. Resnick NM, Yalla SV. Geriatric incontinence and voiding dysfunction. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's urology. 7th ed. Philadelphia (PA): W.B. Saunders Co.; 1998. p. 1045.
8. Nicolle LE. Urinary tract infection in long-term-care facility residents. Clin Infect Dis 2000; 31:757–761.
9. Lindberg U, Hanson LA, Jodal U, et al. Asymptomatic bacteriuria in schoolgirls. II. Differences in escherichia coli causing asymptomatic bacteriuria. Acta Paediatr Scand 1975; 64:432–436.
10. Johnson TM 2nd, Ouslander JG. Urinary incontinence in the older man. Med Clin North Am 1999; 83:1247–1266.
11. Hu TW, Igou JF, Kaltreider DL, et al. A clinical trial of a behavioral therapy to reduce urinary incontinence in nursing homes. Outcome and implications. JAMA 1989; 261:2656–2662.
12. Eustice S, Roe B, Paterson J. Prompted voiding for the management of urinary incontinence in adults. Cochrane Database Syst Rev 2002; CD002113.
13. Ouslander JG, Blaustein J, Connor A, et al. Pharmacokinetics and clinical effects of oxybutynin in geriatric patients. J Urol 1988; 140:47–50.
14. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 1994; 83:12–18.
15. Bhatia NN, Bergman AM, Karram MM. Effects of estrogen on urethral function in women with urinary incontinence. Am J Obstet Gynecol 1989; 160:176–181.
16. Wells TJ, Brink CA, Diokno AC, et al. Pelvic muscle exercises for stress urinary incontinence in elderly women. J Am Geriatr Soc 1991; 39:785–791.
17. Kobayashi S, Tang R, Shapiro E, Lepor H. Characterization and localization of prostatic human alpha 1 adrenoceptors using radioligand receptor binding on slide-mounted tissue section. J Urol 1993; 150:2002–2006.
18. Lepor H, Auerbach S, Puras-Baez A, et al. A randomized multicenter placebo controlled study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. J Urol 1992; 148:1467–1474.
19. Andersen JT, Ekman P, Wolf H, et al. Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo controlled study. Urology 1995; 46:631–637.
20. Hasan ST, Robson WA, Pridie AK, Neal DE. Transcutaneous electrical nerve stimulation and temporary S3 neuromodulation in idiopathic detrusor instability. J Urol 1996; 155:2005–2011.
21. Bosch JL, Groen J. Sacral nerve neuromodulation in the treatment of patients with refractory motor urge incontinence: long-term results of a prospective longitudinal study. J Urol 2000; 163:1219–1222 .
22. Appel RA. Collagen injection therapy for urinary incontinence. Urol Clin North Am 1994; 21:177–182.

Why Elder Abuse Continues to Elude the Health Care System

Fay S. Kahan, A.C.S.W.[1], and Barbara E.C. Paris, M.D.[2]

Abstract

Elderly men and women of all socioeconomic and ethnic backgrounds are vulnerable to mistreatment, and most often it goes undetected. For many elderly victims of abuse, the hospital is the only potential site for outside contact and support. An elder abuse program has been created at The Mount Sinai Hospital in New York City, and funding was granted to assist victims with compensation claims; provide counsel and advocacy for victims; and provide support via ongoing telephone contact and referrals to community agencies. Simultaneously, hospital-wide educational seminars and rounds have provided the staff and students with information concerning detection of abuse and neglect.

Over a 2-year period, 182 cases were identified and assessed. More than 50% of these cases involved patients with a diagnosis of memory impairment. Five percent of the cases involved a long history of domestic violence. In most cases a family member was identified as the abuser, and in a majority of instances the victim either denied the suspected abuse or tried to rationalize the behavior of the abuser. Patients were afraid of reporting abuse or changing their situation, despite being informed of possible resources.

To combat this escalating problem in our growing elderly population, interdisciplinary collaboration between physicians and social workers is often crucial. Communication via the medical record can be key to monitoring patients in the community. There also needs to be ongoing education of all hospital staff in an effort to continually heighten awareness of this problem.

Key Words: Elder abuse, elder neglect, elder mistreatment, detection of abuse.

As the aging population grows, the problem of elder mistreatment is escalating. It is well known that elderly men and women of all socioeconomic and ethnic backgrounds are vulnerable to mistreatment, most of which goes undetected. Currently, elder abuse affects from one to ten percent of the population in the United States (1). According to an executive summary of a National Elder Abuse Incidence Study, conducted in 1996, a total of 449,924 elderly persons, aged sixty and over, experienced abuse and/or neglect in the community. However, 84% of the cases are not reported to any adult protective services agency (2).

For many elderly abuse victims, the hospital setting is the only potential source of outside contact and support. Health care professionals, therefore, may be the only people in a victim's life who have the opportunity to recognize the abuse and offer help. Despite this, it is felt that medical staff are not adequately trained in detecting elder mistreatment or making appropriate referrals to social workers and protective service agencies. Interestingly, a study done in Michigan showed that, between 1989 and 1993, some of the highest physician-reporting rates were found in counties with low physician-to-population ratios. These data suggest that rural primary care physicians are more apt than specialists to detect and report elder mistreatment (3). Indeed, few specialty training programs specifically educate their house staff about family violence. Continuing medical education programs rarely address this issue in any systematic way (4).

The Mount Sinai Hospital Elder Abuse Program

In October of 1998, the Department of Social Work Services at The Mount Sinai Hospi-

---

[1] Social Worker, Elder Abuse Coordinator and [2] Associate Professor of Medicine and Geriatrics, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Fay S. Kahan, A.C.S.W., Department of Geriatrics, Box 1070, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

The Elder Abuse Program is supported by a grant from the New York State Crime Victims Board.

Presented at the First World Conference on Jewish Services for the Elderly, Jerusalem, Israel, November 1999.

tal, a voluntary teaching hospital located in New York City, was awarded a grant by the New York State Crime Victims Board to provide direct services to elderly abuse and neglect victims at The Mount Sinai Hospital, which has a sizable elder patient population. This funding has supported the creation of the Mount Sinai Hospital Elder Abuse Program. It is coordinated by a social worker with a master's degree, who assists with compensation claims, counsels victims, maintains follow-up telephone contacts, accompanies victims to legal offices, provides information and referral services, and advocates for the needs of the victims. The Elder Abuse Program social worker collaborates with a geriatrician who is an expert in the field of elder abuse.

Not surprisingly, there have been many obstacles to identifying cases within the hospital setting, and it was felt that staff education was essential to raise awareness of the problem of elder abuse and neglect. Prior to acting as advocates for elder abuse patients, the staff needed to be educated about elder abuse/neglect and the process of identifying and referring possible victims to the program. Various teaching tools have been used to increase awareness, including: the distribution of printed brochures about the Elder Abuse Program; presentations at medical grand rounds and social work rounds; and informal discussions with medical staff, nurses, patient representatives and other staff. In these presentations, definitions of elder abuse and neglect (Table 1) (5), assessment tools and intervention strategies are discussed. A pocket-sized laminated card (6), listing helpful questions in eliciting information from patients, was developed and is distributed widely (Table 2). Through these efforts, medical and social work students are becoming aware of this growing problem early in their careers.

TABLE 1

Definitions of Elder Abuse

Physical Abuse — The infliction of physical pain or injury such as slapping, pushing, sexually molesting, etc.

Psychological Abuse — The infliction of mental or emotional distress such as threats, intimidation, verbal attacks, etc.

Financial Abuse — The illegal or improper use of funds or other resources.

Active Neglect — A conscious and intentional attempt to inflict physical or emotional distress by refusing or failing to fulfill a caregiving responsibility, such as withholding food or medication.

Passive Neglect — An unintentional failure to fulfill a caregiving responsibility, such as not providing food or health-related services because of inadequate knowledge or caregiver's own infirmity.

Case Example

Mr. R. was a ninety-eight-year-old widowed Hispanic man, living with his son. They resided in a home privately owned by Mr. R. in New York City. Mr. R. was a retired presser, supported by Social Security and a pension. He had medical insurance through a managed care Medicare provider.

Mr. R. was initially seen at The Mount Sinai Hospital Coffey Geriatrics Practice in December 1997 for routine medical care. His medical problems included dementia, emphysema, vitamin B12 deficiency, visual and hearing impairments, a gait disorder and degenerative joint disease. His medical history was significant for pneumonia, a tibial fibula fracture and alcohol abuse. His subsequent visits were sporadic; however, in May 1999 his son brought him to the Coffey Geriatrics Practice because of swelling and redness of his right hand. Mr. R.'s personal hygiene was poor and he appeared rather thin. He was evaluated by the nurse practitioner and referred to the Elder Abuse Program social worker for further assessment. The social worker, along with a Spanish-speaking

TABLE 2

Elder Abuse / Neglect Screening Assessment Tool

1. Has anyone ever hurt you?
2. Does anyone ever talk or yell at you in a way that makes you feel bad about yourself?
3. Has anyone ever taken anything from you or used your money without permission?
4. Are you afraid of anyone or has anyone ever threatened you?
5. Has anyone ever refused to help you?
6. Do you feel that your food, clothing, and medications are available to you at all times?
7. Are you able to go out of your house when you wish to do so?
8. Do you get to see other relatives and friends?
9. Do you have ready access to a telephone?
10. Do you live with anyone or have any close family members who abuse drugs and alcohol or have a psychiatric or emotional illness?

Adapted from: Elder mistreatment guidelines for health care professionals: detection, assessment and intervention. New York: Mount Sinai/Victim Services Agency Elder Abuse Project; 1988 (6).

medical office assistant, interviewed Mr. R. without the son being present in the room. Mr. R. was somewhat tangential and repetitive, but was able to provide information. He reported being dependent on his son for assistance with most activities of daily living and financial management, for which his son had power of attorney. He was quite isolated, with almost no social or family contact apart from his son. He admitted that his son was verbally abusive, neglectful and threatening, specifically stating that his son would lock him out of his own home. Mr. R. was evasive about episodes of physical abuse, stating, "I'm not here to answer questions."

Based on Mr. R.'s injury, his general appearance, and concerns about elder abuse, the social worker, in collaboration with the medical team, decided to admit him for further evaluation. Over time, Mr. R. revealed, usually to Spanish-speaking staff, that his son had been physically abusive to him. Although Mr. R. was amenable to a short-term rehabilitation program in a nursing facility, his managed care plan would not cover this, because he had no medical needs. Despite several meetings with Mr. R. advising him of safety risks in his home, he chose to return home to the care of his son, stating "Family is family."

Discharge plans by the team included:

1. A referral to Protective Services for Adults for evaluation of Mr. R.'s safety in the home, with oversight by the Mount Sinai Hospital Elder Abuse Program.

2. A referral to the Visiting Nurse Service for nurse and social work assessments in the home.

3. Frequent follow-up appointments and monitoring by the Elder Abuse Program and staff at the Coffey Geriatrics Practice.

Mr. R. was brought by his son to the Coffey Geriatrics Practice for his initial follow-up appointment after his discharge from the hospital. The son was quite angry and somewhat threatening to staff because a Protective Services for Adults caseworker had visited their home earlier in the day. Although Mr. R. appeared anxious about his son's anger, he repeatedly stated that he wanted to go home with him. The staff allowed the son to verbalize his anger while discussing concerns about the patient's safety. They reinforced the need for regular follow-up care. The medical staff agreed that Mr. R. had no current signs of physical abuse and had not had any further weight loss. He was therefore sent back home to the care of his son. The Protective Services for Adults caseworker was contacted after Mr. R.'s initial follow-up visit. He reported that Mr. R.'s home was clean and that the son was cooperative during his visit. He therefore closed the case, even though he was concerned about the son's evasiveness with respect to Mr. R.'s finances. The Elder Abuse Program social worker also spoke with the visiting nurse, who initially had difficulty arranging a home visit with Mr. R. and his son, but had finally been able to gain entry to the home. He did not detect any significant problems, but felt that Mr. R.'s son had a limited understanding of his father's deficits. The visiting nurse saw Mr. R. twice and was allowed one more visit by Mr. R.'s managed Medicare program; however, phone calls made to arrange a follow-up visit were never returned by the son.

Approximately two months later, Mr. R. was brought to the Coffey Geriatrics Practice by his son for a routine follow-up appointment. The social worker greeted them in the waiting area. Mr. R. immediately began telling the social worker that he was frequently left alone at home ("I can only see other people by looking out the window"). Despite attempts to calm Mr. R. and reassure him that this would be discussed in a private area, his anger escalated. His son became irate and they both left the appointment without further evaluation. Follow-up telephone messages were left for the son to bring Mr. R. back, but they went unanswered.

An attempt was made by the Elder Abuse Program social worker to re-refer the case to Protective Services for Adults; however, they did not feel that Mr. R.'s situation had changed from their initial assessment. The Protective Services for Adults director and intake supervisor were contacted, since the medical team felt strongly that a reevaluation was advisable. The intake supervisor reported that telephone contact had been made with the son, who indicated that the home situation was stable, with Mr. R. receiving food from Meals-on-Wheels. The son also claimed that he took his father outdoors several times a week. Additionally, the assistant director of Protective Services for Adults spoke with the son, via telephone, about follow-up medical care for Mr. R. The son indicated that Mr. R. was resistant to returning to the Coffey Geriatrics Practice, and that they would be seeking alternate medical care. Despite these coordinated efforts by the Elder Abuse Program social worker and the staff at Protective Services for Adults, the case was lost to follow-up.

Epilogue

In October 2001, the Elder Abuse Program social worker was consulted by the inpatient geriatrics unit medical team on a one-hundred-year-old Hispanic man brought in after sustaining a fall at home. Staff was concerned about physical abuse and neglect, as the patient was bruised and had poor personal hygiene. The Elder Abuse Program social worker immediately recognized Mr. R., noting that he was more cachectic, less alert, and more cognitively impaired than he had been two years previously. Mr. R. was unable to provide any information (even with Spanish-speaking staff), given his weakened state and poor mental status.

The medical staff and the Elder Abuse Program social worker met with the son, who appeared to minimize the extent of his father's physical and cognitive deficits. The son related that, despite Mr. R.'s visual deficits and poor physical condition, he was able to ambulate independently in their home. He stated that Mr. R. had episodes of falling, but medical care was not sought, as Mr. R. would not have wanted to be brought to a hospital. Mr. R.'s son called 911 after this fall because Mr. R. had seemed "dazed."

Discharge options were discussed. Mr. R.'s son was amenable to short-term geriatric rehabilitation if Mr. R.'s insurance covered it, but would not agree to permanent nursing home placement, given the high costs of this option.

Unfortunately, Mr. R. aspirated and died a few days later in the hospital.

Results of Elder Abuse Program Initiatives

1. Between January 1999 and November 2001, one hundred and eighty-two (182) cases were identified and assessed.

2. The majority of referrals have been from social workers in the emergency room, the inpatient geriatrics unit, and physicians and nurse practitioners in the Home Visiting Doctors program.

3. In approximately 50% of referred cases, there was a diagnosis of memory impairment.

4. Referrals primarily involved suspicion of verbal abuse, neglect and financial exploitation. Very few referrals for cases of physical or sexual abuse were received.

5. Nine cases (5%) of accepted cases involved a long history of domestic violence.

6. A family member was usually the abuser, although there were approximately 15 cases in which home attendants were suspected of abuse.

7. In many cases, victims either denied the suspected abuse was taking place or tried to rationalize the behavior of the abuser, especially if this was a family member.

8. Patients were fearful of reporting abuse or changing their situation, despite being informed of possible resources.

Based on the needs of the identified cases, the following interventions were made by the Elder Abuse Program:

1. Referrals of victims for follow-up medical care, since some of these individuals had not had medical care for years.

2. Ongoing social work involvement for continued counseling.

3. Reassurance telephone calls to monitor victims' safety in the community.

4. Home visits to victims who were too frail to come to the Coffey Geriatrics Practice.

5. Referrals of victims to community agencies for more intensive case management and additional services, with oversight by the Elder Abuse Program.

6. Involvement of Protective Services for Adults for guardianship proceedings, in collaboration with the Elder Abuse Program.

7. Placement of victims in assisted-living facilities or nursing homes.

Discussion

Although there have been multiple initiatives to educate medical and other hospital staff about the signs and symptoms of elder abuse and neglect, it is likely that some patients experiencing mistreatment are still not being referred to the program. Feelings of shame, guilt and fear may be responsible, or partially responsible, especially if a family member is the abuser (7). One should take into account the perspectives of both the patients and the health care providers in considering the reasons for this. Additionally, it is well known that domestic violence victims as well as elder abuse victims are reluctant to change their situations for fear of being alone or placing the abuser at risk (e.g., homelessness, incarceration). While some victims may be willing to discuss their abusive situations with a health care provider, victims tend to minimize the seriousness of the abuse and display tremendous loyalty to their abusers. Victims are generally not willing to take legal action against a family member. Many victims prefer tolerating the abuse to losing close personal ties to family members. Often, the abuser is the only person the patient can rely on for assistance with the activities of daily living. As such, the victim may fear that institutionalization, such as nursing home placement, is the only alternative solution.

In the same vein and as pointed out in the literature (8), many health care professionals are either unaware of the prevalence of abuse or are reluctant to ask their patients about domestic violence. This applies to elder mistreatment as well. Talking about family violence with patients has been characterized as "opening a Pandora's box" (9). Practitioners may feel helpless about their inability to "fix" the situation or influence a patient's decision. Feelings of anger and blame are natural reactions to reports about abuse, especially when the practitioner feels powerless to change them. These responses may be even more pronounced for health care professionals who believe they are supposed to "treat" the problem. Additionally, the pressures and time constraints of medical practices leave little time to delve into the complex issue of family violence.

Another significant factor impacting medical staff is concerns and doubts about patients' safety if they are discharged to abusive environments. From the hospital's standpoint, given economic considerations, it may be difficult to admit these patients, as insurance companies will not reimburse for so-called "social admissions." We need to be aware of the possibility of retaliation on the part of the abuser and must have safety measures in place, should the victim be punished by the abuser for exposing the mistreatment. The health care provider should ensure that a victim has access to a telephone and can call for emergency assistance. It is necessary to explore with the victim whether there may be a safe place to stay or if there are other social supports available, even on a temporary basis. Alternative housing options can also be discussed with the victim. The concern of staff for its own safety may be another factor hindering willingness to uncover abuse. A health care provider may feel frightened or even threatened by an abuser, which may make it difficult to question a victim. Safety measures need to be considered, to decrease possible harm to both health care providers and patients. In the case of Mr. R., his son was loud and threatening. Those staff members who were not in direct contact with Mr. R. and his son were alerted to the tension and were available to contact the security department, if it became necessary.

Often, patients themselves will choose to return to environments deemed unsafe. In these situations, staff members struggle to determine whether victims are exercising poor judgment or have crossed over the fine line to decisional incapacity. A patient's ability to report or describe abuse may be affected by language or cognitive deficits. In these cases it is important to observe behavioral changes in determining the patient's risk and ability to make a decision (10).

A patient's right to self-determination is the underlying factor in states where there is no requirement for mandatory reporting of abuse to government agencies. In these states, it is argued that victims with mild cognitive and memory impairments can still make their own decisions about remaining in abusive situations. Health care providers may feel uncomfortable with a patient's decision to remain with the suspected abuser, but may need to accept this and continue to help the victim strive to improve the situation through ongoing counseling.

The isolation of elderly victims is an additional barrier to the reporting and detection of mistreatment. Often, medical visits are the only times victims leave their homes or are allowed out by the abuser. Abusers tend to isolate victims by denying them access to friends and telephone. In one particular study comparing elder abuse victims with a control group, it was found that abused elders did appear more isolated (11). They tended to have fewer overall contacts and to feel negatively about their social situations. The abuser often prevents or inhibits contact with outsiders through threatening behavior or by creating conflict in order to make visitors feel uncomfortable. Friends or other family members who may be able to intervene in the situation are driven away, allowing the abuser's behavior to escalate. This, in turn, leads to further isolation and makes it even more difficult for the victim to discuss the mistreatment.

Mr. R. was confined to his home because of his functional limitations, but also by his son, who rarely took him out. He was unable to go out independently because of the risk of his falling and his poor eyesight. He had previously participated in a local senior center, but was no longer able to go there on his own. A wheelchair was available to the patient, but he depended on his son to transport him, which was infrequent. Medical appointments were sporadic and Mr. R. was generally brought to the hospital only for emergency purposes. Mr. R. himself complained that the only people he saw were those "out of [his] window." His son clearly isolated him and was insensitive to the negative impact this was having on him.

Cultural diversity among patients provides unique challenges to social service and health care providers. Among various cultural groups, elders have held the traditional position of respect and esteem. If they expect to be cared for by the family that is no longer willing or able, they may become vulnerable to abuse. Family members may become or resentful of their obligations, which can lead to abusive situations (12). Elderly victims may feel embarrassed to divulge information about abuse to a representative of their own community, and even more so to one not of their cultural background. Understanding the risk factors for elder abuse in specific cultures is critical for practitioners working with immigrant families. A victim's inability to speak English and fear of abandonment are factors contributing to an elder's reluctance to talk about the abuse that is being experienced. A common belief among various cultural groups is that outsiders should not know about their affairs. Elder abuse victims, over their lifetime, may have internalized this belief and, additionally, may view American social welfare institutions as alien, thereby making it difficult for practitioners to detect any problems (13). If abuse is detected, the victim may deny it or reject interventions unless offers to help are framed in a culturally sensitive manner. In our efforts to provide services to these patients, we may need to expand our educational efforts and refer cases to practitioners who are from a similar cultural background and speak the same language. The use of interpreters is important and can be a source of support for the victims; however, we need to ensure that accurate information, through the translation process, is obtained. The case of Mr. R. brings to light cultural factors impacting on our interactions with him. Mr. R. was more forthcoming about abuse with Spanish-speaking staff. It was felt that his frequent refrain of "family is family" represented the Hispanic belief that family members should remain together. For non-Hispanic staff working with Mr. R., it was important to learn of the concept of *la familia*, in which the needs of the family unit are greater than the needs of the individual. Pride in the Hispanic family leads to practices of privacy and nonacceptance of outsiders to deal with family problems. The values of loyalty, interdependence and privacy are inherent in this culture, making it difficult for an abuse victim to reveal mistreatment or allow family to be confronted (12).

An additional factor not to be overlooked when working with elderly abuse victims is their own "ageist attitudes" or feelings of self-blame. Often, victims believe that they are responsible for the abuse or that they pose a burden on their caregivers. These feelings frequently lead to diminished self-esteem, with the elderly person feeling that, in a sense, the mistreatment is deserved. In the case of Mr. R., he pointedly stated, "I am a burden to my son."

Health care professionals struggle with their own ageist feelings about the elderly and their caregivers. This can present obstacles to viewing certain actions as abusive in the face of behaviorally challenging patients. Are we as staff sufficiently trained or able to predict which overwhelmed caregiver may be at risk of becoming abusive? Are we sometimes biased in our decisions, given our interactions with the abuser or potential abuser? Staff needs to be proactive in providing counseling and resources to caregivers, in an attempt to avoid any future abuse.

Recommendations

Cases of elder mistreatment can be highly complex, and the development of a "high-risk team" for interdisciplinary collaboration can be helpful to practitioners and elderly patients. Members of the team can bring distinct expertise in detecting problems. Physicians may be able to uncover abuse during physical examinations, when patients may not openly admit to the problem. Victims would also gain comfort in knowing that various members of the health team are aware of their problem and are willing to help. Health care settings should develop ways of identifying those cases considered to be at risk (e.g., "flagging a chart"). Emergency room staff should have a list of patients known to be victims of abuse, as the ER is often the patient's first contact in the hospital. The availability of a 24-hour-a-day social worker or volunteer trained in elder abuse is also important, so that cases can be handled effectively when a patient presents to the hospital.

While victims' services hotlines are available in many states, perhaps hotlines developed specifically for elder abuse could be made available for victims over the age of 60. Counselors would be able to determine if victims are at immediate risk or could be referred for more intensive case management services. In states where mandatory reporting is not required, perhaps a "registry" would be beneficial, whereby victims' names could be registered. Given concerns about confidentiality, this would need to be done with the client's consent. If the current situation destabilizes, the practitioner could then make a formal referral to a protective services agency. Victims themselves could call the "registry" if they feel their safety is at risk.

Managed care providers may be limited in the services that they can provide; however, the severity and escalation of the problem of elder abuse needs to be brought to their attention, so that patients receive appropriate services and counseling. Case management services should be available through the provider, in order for a patient's safety to be monitored in the community.

Of utmost importance is the ongoing education of health care and social service staff. We need to continually heighten the awareness of everyone within the hospital community to the abuse of elders. For example, housekeeping staff have contact with patients and need to recognize inappropriate behaviors and know how to report their observations. Medical students must be made aware early in their careers of the problems associated with abuse of the elderly. Continuing education efforts through grand rounds, seminars and training sessions should be developed to maintain the focus on this growing problem.

Conclusion

Elder abuse is an escalating problem in our society, but one that often eludes us. To protect our elders, health care professionals need to heighten their awareness of this problem and expand their "comfort level" in questioning patients about family violence. The general community also needs to be informed about this problem, so that appropriate services can be developed and provided. The media could play an important part in calling attention to this often undetected social problem.

Acknowledgments

The authors acknowledge the assistance of Judith F. Dobrof, D.S.W., assistant professor, Department of Community and Preventive Medicine, the Mount Sinai School of Medicine, New York, NY.

References

1. Understanding elder abuse: a guide for health care volunteers. New York: United Hospital Fund; 1995.
2. The national elder abuse incident study. In: Administration on aging. Prepared by The National Center on Elder Abuse in collaboration with Westat. Final report, Sept 1998.
3. Rosenblatt DE, Cho KH, Durance PW. Reporting mistreatment of older adults: the role of physicians. J Am Geriatr Soc 1991; 44:65–70.
4. Warshaw C. Identification, assessment and intervention with victims of domestic violence. In: Warshaw C, Ganley AI. Improving the health care response to domestic violence. A resource manual for health care providers. San Francisco (CA): Warshaw C and Ganley AI; 1998. pp. 49–86.
5. Wolf R, Pillemer KA. Working with abused elders: assessment, advocacy, and intervention. Worcester (MA): University Center on Aging, University of Massachusetts Medical Center; 1984.
6. Elder mistreatment guidelines for health care professionals: detection, assessment and intervention. New York: Mount Sinai/Victim Services Agency Elder Abuse Project; 1988.
7. Cammer Paris BE. Violence against elderly people. Mt Sinai J Med 1996; 63:97–100.
8. Gerbert B, Caspers N, Bronstone A, et al. A qualitative analysis of how physicians with expertise in domestic violence approach the identification of victims. Ann Intern Med 1999; 131:578–584.
9. Sugg NK, Inui T. Primary care physicians' response to domestic violence. Opening Pandora's box. JAMA 1992; 267:3157–3160.
10. Baladerian NJ. Recognizing abuse and neglect in people with severe cognitive and/or communication impairments. J Elder Abuse Neglect 1997; 9(2):93–104.
11. Wolf RS, Pillemer KA. Understanding the causes of physical elder abuse. In: Wolf RS, Pillemer KA. Helping elderly victims: the reality of elder abuse. New York: Columbia University Press; 1989. pp. 69–81.
12. Montoya V. Understanding and combating elder abuse in Hispanic communities. J Elder Abuse Neglect 1997; 9(2):5–17.
13. Brownell P. The application of the culturagram in cross-cultural practice with elder abuse victims. J Elder Abuse Neglect 1997; 9(2):19–33.

Required Form for Authors

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal*.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

4. US Federal Employees

I was an employee of the US government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

09/2002

THE
MOUNT SINAI JOURNAL
OF MEDICINE

3 4805 0733458 0
LEVY LIBRARY, MT. SINAI SCHOOL OF MEDICINE

Forthcoming: Grand Rounds

Hypersensitivity Reactions to Drugs: Evaluation and Management
Gillian M. Shepherd
Weill Medical College of Cornell University
New York, NY

Behavioral Cardiology — Has Its Time Finally Arrived?
Thomas Pickering, Lynn Clemow, Karina Davidson, and William Gerin
Mount Sinai School of Medicine

Neurotrophins, Growth Factor-Regulated Genes and the Control of Energy Balance
Stephen R.J. Salton
Mount Sinai School of Medicine

Theme Issues

Ethics 1999 — Ethical Limits of Transplantation
Rosamond Rhodes and Daniel A. Moros, Editors

Available now:

Methadone Symposium – Part 1:2000
Volume 67: Numbers 5 & 6. 125 pages, $40.00

Methadone Symposium – Part 2:2001
Volume 68: Number 1. 78 pages, $25.00

Gastroenterology and Hepatology at The Mount Sinai Hospital 1852–2000
Volume 67: Number 1. Part 1:2000 94 pages $20.00
Volume 67: Number 3. Part 2:2000 89 pages $20.00
Volume 68: Number 2. Part 3:2001 80 pages $25.00

Visit our web page — http://www.mssm.edu/msjournal

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 70 NUMBER 2 MARCH 2003

GERIATRICS

Barbara E.C. Paris and Carol F. Capello, guest editors

PART 2

GUSTAVE L. & JANET W. LEVY
MAR - 5

Elder Abuse: Is Every Bruise a Sign of Abuse? *Maria T. Carney, Fay S. Kahan, and Barbara E.C. Paris* 69

Overview of Geriatric Emergencies *Barbara K. Richardson* 75

Stability of Preferences Regarding Life-Sustaining Treatment: A Two-Year Prospective Study of Nursing Home Residents *Elaine McParland, Antonios Likourezos, Eileen Chichin, Tita Castor, and Barbara E.C. Paris* 85

DEAN'S LECTURE

Neurotrophins, Growth-Factor-Regulated Genes and the Control of Energy Balance *Stephen R. J. Salton* 93

GRAND ROUNDS

Behavioral Cardiology — Has Its Time Finally Arrived? *Thomas Pickering, Lynn Clemow, Karina Davidson, and William Gerin* 101

Hypersensitivity Reactions to Drugs: Evaluation and Management *Gillian M. Shepherd* 113

GENERAL ARTICLES

Meconium Enhances the Growth of Perinatal Bacterial Pathogens *Arda Lembet, Sreedhar Gaddipati, Ian R. Holzman, Richard L. Berkowitz, and Edward J. Bottone* 126

Small Bowel Perforation Secondary to Metastatic Lung Cancer: A Case Report and Review of the Literature *George H. Sakorafas, George Pavlakis, and Kyriakos D. Grigoriadis* 130

Primary Bone Marrow B-Cell Lymphoma: Report of Four Cases *James A. Strauchen* 133

Information for Authors i

Required Form for Authors C3

SAINT BARNABAS HEALTH CARE SYSTEM
Old Short Hills Road Livingston, New Jersey 07039

LIBERTY HEALTHCARE SYSTEM, INC.

Veterans Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by the Mount Sinai Medical Center of New York and has the following affiliates: Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY; Saint Barnabas Health Care System, Livingston, NJ; Newark Beth Israel Medical Center, Newark, NJ; Liberty HealthCare System, Inc., Jersey City, NJ.

Editor-in-Chief
Sherman Kupfer, M.D.

Administrative Assistant
Ron Stein

Associate Editors
Harriet S. Gilbert, M.D.
Leslie A. Kuhn, M.D.
Philip S. Ledereich, M.D.

Assistant Editor for Housestaff
Leora Horwitz, M.D.

Assistant Production Assistant
Mel Meyer

Assistant Editors
Scott H. Barnett, M.D.
J. Hugh Baron, D.M.
David H. Bechhofer, Ph.D.
Constantin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
James L. Breen, M.D.
Donald Brief, M.D.
Daniel Buchbinder, D.M.D, M.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., M.P.H., M.P.P.
William H. Constad, M.D.
Kenneth L. Davis, M.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Jack Hirschowitz, M.B., Ch.B.
Fred M. Jacobs, M.D., J.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M. Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkovitz, M.D.
Dana M. Lewis, M.L.S.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Myron Miller, M.D.
Richard Panush, M.D.
Barbara E. C. Paris, M.D.
Jerome G. Porush, M.D.
Georges R. Ramalanjaona, M.D., D.Sc.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Tibor Rohacs, M.D.
Gregory J. Rokosz, D.O., J.D.
Joshua Rosenblatt, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Harry Schanzer, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Janet B. Serle, M.D.
Phyllis Shaw, Ph.D.
Scott H. Sicherer, M.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson N. Stone, M.D.
Max Sung, M.D.
Jules A. Titelbaum, M.D.
Thomas A. Ullman, M.D.
Richard P. Wedeen, M.D.
Klaudiusz R. Weiss, M.D.

Editorial Board
Barry S. Coller, M.D.
Kenneth L. Davis, M.D.
Panayotis G. Katsoyannis, Ph.D.
Jack G. Rabinowitz, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, Septemb October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-65 Subscription price: individuals (U.S. and Canada), $79 per year; libraries and institutions (U.S. and Canada), $121 per year; individuals (outs U.S. and Canada), $105 per year; libraries and institutions (outside U.S. and Canada), $147 per year. The charge per copy of a single num issue is $25, for a two-number issue is $50. New subscriptions begin with the first issue of the calendar year. Send notice of change of addr 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send addr changes to *The Mount Sinai Journal of Medicine*, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212) 2 6108. Fax (212) 722-6386. e-mail: msjournal@mssm.edu; web page: www.mssm.edu/msjournal. Copyright 2003.

DISCLAIMER: The statements and opinions expressed in *The Journal* by authors and contributors are solely their own and not those of The Mount S Medical Center or *The Mount Sinai Journal of Medicine*. All advertisements are expected to conform to ethical standards, and their appearance does not im endorsement or approval by The Mount Sinai Medical Center and/or *The Mount Sinai Journal of Medicine* of the products with respect to effectiveness, quality safety. The Mount Sinai Medical Center and *The Mount Sinai Journal of Medicine* do not hold themselves responsible for statements made by the author contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in *The Journal* is protected by copyright. In accord with U.S. Copyright law, no part of *The Journal* may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior writte permission to do so. Permission should be requested from The Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574

Elder Abuse:

Is Every Bruise a Sign of Abuse?

Maria T. Carney, M.D.[1], Fay S. Kahan, A.C.S.W.[2], and Barbara E.C. Paris, M.D.[3]

Abstract

Each year, between 1 1/2 and 2 million older adults in the United States are abused. Physicians are in an ideal position to recognize, manage and prevent elder mistreatment. This article uses a problem-solving format to discuss a case report. This case, which spanned two years, highlights the true difficulty in recognizing and managing elder mistreatment.

Key Words: Abuse, neglect, mistreatment, aging, frailty, elderly, elder abuse.

Introduction

THE ELDERLY are the fastest growing segment of the population in the United States (1). Consequently, mistreatment of the elderly is an escalating problem. In fact, it is estimated that each year, between 1 1/2 and 2 million older adults are abused (2). Physicians are in an ideal position to recognize, manage and help prevent elder mistreatment and neglect. To illustrate this, we present a problem-solving format to discuss a case report. This case, which spanned two years, highlights the true difficulty in recognizing and managing elder mistreatment. The value of a multidisciplinary approach is emphasized, in order to achieve optimal care of these difficult cases.

First Office Visit (8/96)

An 84-year-old Hispanic woman arrives at the outpatient office one hour late for her appointment; she is accompanied by her son and his female friend. They report a history of confusion of two years' duration, a growing bulge in the stomach, tremors, and recent bed wetting. Although the patient reportedly has never previously been to a physician, she is not in any distress and appears to be comfortable and cooperative with staff and family. She is alert and oriented to person and time, but not to place. She has resting hand and lip tremors that stop on intention. She has a large, non-tender protruding abdominal mass with bowel sounds, but it is not completely reducible. She has a shuffling gait. Laboratory studies and electrocardiogram are performed. Both dementia and Parkinson's disease are suspected at this time. The patient is diagnosed as having a ventral hernia. She is given a one-week follow-up appointment to review laboratory results.

Discussion

It is unsettling that an 84-year-old woman with multiple medical complaints has never seen a physician. Clarification of the patient's functional status and social situation, including caregiver information, is needed at this point. Some questions to consider are:

Why is it urgent for the patient to be seen?
Is there a new stressor requiring medical attention?
Has the patient's functional status worsened over days, months, or years?
Is the caregiver qualified to provide all the care?

From the Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY.

[1]Attending, Division of Geriatrics, Winthrop University Hospital, Mineola, NY and Assistant Professor of Clinical Medicine, SUNY at Stony Brook Medical School, Stony Brook, NY; and [2]Elder Abuse Coordinator and [3]Associate Professor, Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Maria T. Carney, M.D., Winthrop University Hospital, Division of Geriatrics, 222 Station Plaza North, Suite 518, Mineola, NY 11560; Email: mcarney@winthrop.org

This manuscript has been updated as of August 5, 2002.

What is the role of the son's friend?

During the physical examination, one can request that the family step outside, and use this opportunity to interview the patient alone. One can initiate conversation with a routine question such as "How are things at home?" and follow it with more specific questions, such as those listed in Table 1 (3, 4).

TABLE 1
Questions to Elicit Elder Abuse (3, 4)

Physical Abuse:	Are you afraid of anyone at home? Have you been struck, slapped or kicked? Have you been tied down or locked in a room? Has anyone touched you without your permission?
Emotional Abuse:	Do you ever feel alone? Have you been threatened with punishment, deprivation, or institutionalization? Have you received the "silent treatment"? Have you been force fed? What happens when you and your caregiver disagree?
Neglect:	Do you lack aids such as eyeglasses, hearing aids, or false teeth? Have you been left alone for long periods? If you need assistance, how do you obtain it? How do you get help?
Financial abuse:	Does your caregiver depend on you for shelter or financial support? Has money been stolen from you?

Second Office Visit (9/96)

The patient has been having difficulty ambulating since the last visit, and the tremors continue. Laboratory values are within normal limits except for borderline low vitamin levels. Levodopa / carbidopa is initiated for the treatment of Parkinson's disease. Dementia is still suspected, but the etiology is still unclear and requires further evaluation.

The social worker ascertains that the son is partially disabled and unemployed, and depends on his mother for housing and finances. He is able to help her with activities of daily living. The patient expresses concern about her increasing dependency. The social worker initiates a home evaluation.

The home-care team finds that the patient is living in an apartment without heat, electricity, or food, and begins to investigate financial resources and support services for the patient. Adult Protective Services is also notified.

Discussion

A home evaluation can provide a better understanding of the social environment (5). In this case, a home evaluation was initiated by the physician, who consulted with a social worker. The American Medical Association (AMA) has emphasized that physicians "are in an ideal position to recognize, manage, and prevent elder mistreatment" (2). A 1991 report from Congress suggests that 1.5 – 2 million older adults in the United States are abused annually. It is estimated that only 1 of 14 elder mistreatment cases is reported to a public agency (2). A majority of states have mandatory reporting laws that require health-care workers to report suspected abuse of elderly persons to an official state agency, usually Adult Protective Services (6). In many states the "suspicion" of abuse, without any proof, is grounds for reporting, and the physician does not have to prove anything (7). Many states grant immunity to physicians who report their suspicions in good faith, and often the reporter remains anonymous. Moreover, physicians should be aware of a potential liability if cases of domestic violence are not detected, diagnosed or reported (7). The goal in contacting Adult Protective Services is to determine what services might benefit the elderly person living in the community, rather than implicating the potential abuser.

Third Office Visit (10/96)

The physician performs an assessment of the patient's cognitive abilities. She has completed grammar school education in Puerto Rico. The patient scores 19 out of a possible 30 points on a Mini-Mental State Examination (MMSE). Of interest, the sentence the patient wrote, when translated into English, was "I am hungry." The patient's tremors improved with levodopa / carbidopa, which helps to confirm the diagnosis of Parkinson's disease. Parkinson's disease explains increased disability in this patient anc may be the cause of cognitive impairment.

Adult Protective Services, in conjunctior with Home Care Services, arranges for a hom health aide and Meals on Wheels. Further investigation by the social worker reveals that the patient has lapsed Medicaid benefits. The social worker begins a process of reapplying in an effort to restore Medicaid benefits.

The physician receives a call from the home health aide stating that the son had been picked up in a "drug raid," but had been released. There were no further legal repercussions from this event, and the son was not charged with any wrongdoing.

Discussion

Patient safety is foremost at this point. Does the patient appreciate the unsafe situation in which she may be living? Does she have decision-making capacity? Clarification of her comprehension of the situation, choices she may have, understanding of risks / benefits, and her wishes are necessary at this point. At this time, the physician believed that the patient had decision-making capacity. The patient stated that she wanted to stay in her home and denied any problems at home.

This patient's MMSE score suggests cognitive impairment. The MMSE examines six different domains, including orientation, registration (capability of immediate repetition of words or instructions), attention and calculation, recall, language, and constructional ability. In population-based norms, lower median scores on the MMSE were found among adults with 8 years of schooling or less (as is true of our patient), than among those with at least 9 years of schooling (8). Thus, this patient's low level of education may be a complicating factor in using this test as a screen for cognitive impairment. However, it is likely that she has some dementia, which puts her at increased risk for abuse. Indeed, a high prevalence of dementia exists in abuse and neglect cases involving the elderly (9).

Authors describe four types of elder abuse: physical, emotional, financial, and neglect (Table 2) (3, 4, 10, 11). Yet many authorities prefer to avoid terms such as abuse or neglect, and describe a situation as inadequate care of the elderly or mistreatment of the elderly, which allows for acts of omission and commission (12, 13).

This patient has multiple risk factors for abuse and neglect, including functional and cognitive impairment, which makes her dependent on her son, with whom she shares a home (Table 3) (10, 13). The son, who is the main caregiver to his mother, has a history of disabling head trauma and is possibly using illicit drugs. The patient needs to be informed about the incidence of mistreatment of the elderly and the tendency for it to increase in frequency and severity over time (14), as well as its association with a high risk of death (15). Relief of caregiver stress is one avenue to pursue to protect the patient. Support groups, day-care centers, alternative living arrangements, disability benefits, and help from other family members would also achieve some relief of stress (10). The son needs his own medical and social service evaluation, which may enable him to receive disability benefits and provisions for his support.

TABLE 2

Types of Elder Abuse (3, 4, 10, 11)

Physical Abuse — includes hitting, grabbing, slapping, or causing bodily injury, including sexual abuse.

Emotional Abuse — verbal and nonverbal insults, humiliation, infantilization, and threats (experiencing at least 10 episodes in preceding year).

Financial Abuse — theft (social security checks, pensions), misappropriation of funds, and coercion (changing a will or deed).

Neglect (Passive or Active) — failure of a caregiver to provide basic care to a patient, typically involving assistance with the activities of daily living.

TABLE 3

Risk Factors for Elder Abuse (10, 11)

Poor health and functional impairment of the elderly
Cognitive impairment of the elderly
Substance abuse or mental illness of the abuser
Dependence of abuser on victim
Shared living arrangement
External factors causing stress
Social isolation
History of violence in a relationship
Web of dependency by either caregiver on elder or elder on caregiver
Lack of support systems

Two Months Later (12/96)

The visiting nurse calls the outpatient office to report bruises on the patient's arms. On examination, there are old small bruises as well as new areas of redness surrounding these ecchymoses on both forearms. The patient has lost 4 kilograms since her last visit two months ago, despite receiving "Meals on Wheels." The patient is examined alone by this physician, who speaks the same language, and separately by the social worker, who utilizes a translator who is available at the outpatient practice. In both interviews the patient denies being treated poorly, hit, pushed or physically injured in any way. She states that food is always available. She reassuredly states that her son takes good care of her and that she wants to go home.

The son is interviewed and denies any problems. Despite this, he appears restless, anxious and eager to leave. On questioning, the home health aide states that food is often lacking in the home, as the son eats the meals delivered to the patient. The aide has never witnessed physical abuse.

At this time the medical staff believe the patient's bruises are due to the son physically supporting his mother during ambulation. The staff approaches the patient about other relatives who may be available to assist her and asks about whether she has any interest in living in a nursing home. The patient states that she has other children, but does not know how to contact them. The patient has the capacity to make decisions and refuses to change her living arrangements, despite staff concerns about neglect.

Discussion

Has the situation now escalated from one of neglect to one of physical abuse? It is now necessary to reassess the situation and interview the patient in private, away from the suspected abuser(s), as was done. One should interview caregivers separately and determine if their explanations are similar or possibly discordant (10).

Not every bruise is abuse. Elderly skin may bruise easily. During the physical examination, note the size, shape and location of all injuries (16). Photographing the injuries is helpful for documentation (17). Be suspicious of multiple injuries in various stages of healing (10). Look for alopecia, pressure ulcers, welts, scars, abrasions, burns, lacerations, and fractures (16). This patient not only has fragile skin, but is also at risk for falls and trauma secondary to Parkinson's disease, and requires support to ambulate. The son should be educated on how to adequately support his mother in order to minimize trauma.

The staff may face additional challenges when interacting with the patient and caregiver, due to a language, cultural and/or educational barrier. The limited education of the patient, the head trauma history of the son, and the fact that most of the clinic staff did not speak the same language as the patient provide additional challenges. Cultural differences may further compound the difficulty of the staff in comprehending the patient's choice of remaining in an unstable environment. According to Montoya in "Understanding and Combating Elder Abuse in Hispanic Communities," the most important and powerful institution among Hispanics is *la familia* — the family (18). Family loyalty and sacrifice, interdependence, and privacy are values and rules that have protected, empowered, and sustained Hispanics through good times and bad times.

If, at this point, the patient acknowledges mistreatment and is willing to accept assistance, discuss the options for ensuring safety (16). These include admission to a hospital for the sake of safety; placement in a nursing home, adult home, or assisted-living residence; and a court order of protection. If the patient refuses assistance and has decisional capacity, educate him/her about available support services. Provide emergency contact numbers for abuse hot lines, social services, public legal services and local victim services / agencies. If elder abuse is strongly suspected and the patient lacks decisional capacity, guardianship arrangements should be initiated.

Two Months Later (2/97)

The visiting nurse calls the physician to report new abrasions on the patient's buttocks, and small ecchymoses on the dorsum of the hands, bilaterally. The patient is urgently seen again. A multidisciplinary team meeting is held with the outpatient medical and team staff, a social worker and nurse from the home-care agency, and the Adult Protective Services case worker and supervisor. Transfer of financial management is discussed. Adult Protective Services decides to take over financial management of the patient's funds in order to prevent further neglect. Home aide hours are increased to twenty-four hours, seven days a week, and the patient is enrolled in a day-care program.

The community health-care team remains very anxious and repeatedly reports to this physician all potential evidence of abuse. The home-care nursing supervisor requests that the patient be removed from her home against her will and be hospitalized for safety and eventual placement.

Discussion

To comprehensively evaluate elder abuse, a multidisciplinary approach is vital. Periodic team meetings facilitate the management of these complex patients. The team in this case includes a physician, nurse, nurse-practitioner, office-based social worker, community-based social worker, visiting nurse, and Adult Protective Services case worker and supervisor. It is important to keep the care team objective and unified. Issues of staff anxiety, fear of patient injury and legal ramifications need to be addressed. Heightened emotions can create a division in the team, often pitting outpatient staff against home-care staff.

The staff maintains involvement and provides as much care and safety as are accepted by the patient and family. It is important for a health-care provider to remain accessible to the potential victim, who may reject offers of assistance. Victims frequently fluctuate between stages of denial and acknowledgment of the abusive situation (19). Access can be maintained through more frequent visits to the doctor, as was done in this case, or via telephone monitoring.

In this case, one may continue to question whether the patient has the ability to make the decision to stay home. The outpatient staff, based on the patient's apparent understanding of the choices, risks / benefits and ability to defend her judgment, believed the patient has the capacity to make decisions about her living arrangements. The home care team was not in agreement with this decision. They believed her cognitive impairments were hindering her decisions and that she was unsafe at home. The team became increasingly uncomfortable with being involved in her care. They continued to want to admit her into the hospital, which in their view would be safer than her home.

Family Office Visit (8/97)

Two other children (a son and daughter), previously reported by the patient to be estranged, make a surprise visit to the office and discuss their family situation, fears about their stepbrother (the patient's son) and concerns of his maltreatment of their mother. They suspect illicit drug use by the stepbrother, but have no evidence. They suspect he is using her money to support his behavior, as he has no income himself.

Discussion

Why is this family, who were so passive in the past, now actively concerned? What has changed to make them come to see their mother's physician? One must be concerned about patient confidentiality in dealing with "unknown" family members. Would the patient allow her physician to speak to these family members? At this time, it was important to listen to these family members, but not to breach the patient's confidentiality without obtaining the patient's permission. The family provided information. Their concerns were acknowledged and were to be evaluated.

Eight Months Later (4/98)

The mother and son do not come into the office that winter. Subsequently, they report that, over the past several weeks, ambulating has become progressively more difficult and the tremors have become more severe, despite a neurologist's involvement and adjustments in medication dosage. She is no longer able to participate in discussions due to increased lethargy. The son is unable to care for her. The patient is admitted to the hospital to be evaluated for a change in mental status. She is found to be dehydrated.

During the mother's hospitalization the son's impairments become more evident. He lacks the ability to comprehend the overall situation. He easily becomes angry, blames the medical staff for his mother's situation and repeatedly threatens their physician verbally. Multiple discussions are held with the family members about the patient's condition and disposition. As the patient is now incapable of participating in these discussions, it is decided to discharge her to a nursing home, which is felt to be the safest option. In the nursing home, the patient's mental status improves and she begins to eat more on her own. The family visits her regularly.

Conclusion

This physician and office staff felt great frustration throughout the two-year course of this situation. Every office visit left the medical staff on edge, not quite sure if physical abuse was occurring. Were the injuries due to aging frail skin in a patient with Parkinson's disease, and a concerned caregiver doing his best despite his own impairments? Or were the injuries secondary to physical abuse by a caregiver with drug abuse problems, who possibly grew up with a family history of violence? As every bruise is not caused by abuse, it is very important to always think broadly in analyzing each circumstance. In this way one may provide optimal care, avoid false accusations and provide for the safety of the patient.

In this case, initially, there was concern that physical abuse was occurring. However, at each visit the patient denied this, and her injuries could be explained by her medical conditions and impaired function. Despite her denials, the staff acknowledged the risk and potential for abuse to develop. After each office visit, the staff was fearful that the patient was returning to an unsafe situation. The diagnostic challenge never diminished; each complaint and injury required close, frequent and objective evaluation, without at the same time antagonizing the patient or her family. By not openly accusing the son, the staff was able to evaluate the social situation and provide much-needed home services, activate Medicaid benefits, and enroll the patient in a day program, while respecting the patient's wish to stay at home for as long as possible.

Elder neglect, as in this case of a patient's and caregiver's physical and mental inabilities to obtain or provide adequate care, is a deeply complex situation. The reality is that progress can be slow and diagnostic certainty may be lacking. In order to achieve resolution, the staff must be patient and be supportive of each other. And they must be prepared to gather and evaluate the evidence, while maintaining respect for patient autonomy and the family's sensitivities.

References

1. Bell F, Wade AH, Goss SC. Life Tables for the United States Security Area, 1900–2080. Actuarial Study 107. Social Security Administration. Washington, DC. 1993. Publication 11-11536.
2. American Medical Association. Diagnostic and treatment guidelines on elder abuse and neglect. Chicago (IL): American Medical Association; Oct 1992.
3. Kleinschmidt KC. Elder abuse: a review. Ann Emerg Med 1997; 30:463–472.
4. Paris BEC, Meier D, Goldstein T, et al. Elder abuse and neglect: how to recognize warning signs and intervene. Geriatrics 1995; 50:47–51.
5. Scanameo AM, Fillit H. House calls: a practical guide to seeing the patient at home. Geriatrics 1995; 50:33–39.
6. Ramsey-Klawsnick H. Assessing physical and sexual abuse in health care settings. In: Baumhover LA, Beall SC. Abuse, neglect, and exploitation of older persons. Baltimore (MD): Health Professions Press; 1996. pp. 67–87.
7. Stiegel LA. Recommended guidelines for state courts handling cases involving elder abuse. Washington (DC): American Bar Association; 1995.
8. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. JAMA 1993; 269:2386–2391.
9. Dyer CB, Pavlik VN, Murphy KP, Hyman DJ. The high prevalence of depression and dementia in elder abuse and neglect. J Am Geriatr Soc 2000; 48:205–208.
10. Lachs MS, Pillemer K. Abuse and neglect of elderly persons. N Engl J Med 1995; 332:437–443.
11. Pillemer K, Finkelhor D. The prevalence of elder abuse: a random sample survey. Gerontologist 1988; 28:51–57.
12. Fulmer TT, O'Malley TA. Inadequate care of the elderly: a health care perspective on abuse and neglect. New York: Springer Publishing; 1987.
13. Jones JS, Holstege C, Holstege H. Elder abuse and neglect: understanding the causes and potential risk factors. Am J Emerg Med 1997; 15:579–583.
14. Canadian Task Force on the Periodic Health Examination: Periodic health examination, 1994 update. 4. Secondary prevention of elder abuse and mistreatment. CMAJ 1994; 151:1413–1420.
15. Lachs MS, Williams CS, O'Brien S, et al. The mortality of elder mistreatment. JAMA 1998; 280:428–432.
16. Wolfe S. Look for signs of abuse. RN 1998; 61:48–54.
17. Steiner RP, Vansickle K, Lippman SB. Domestic violence. Do you know when and how to intervene? Postgrad Med 1996; 100:103–116.
18. Montoya V. Understanding and combating elder abuse in Hispanic communities. J Elder Abuse and Neglect 1997; 9:5–17.
19. Paris BEC. Violence against elderly people. Mt Sinai J Med 1996; 63:97–100.

Overview of Geriatric Emergencies

Barbara K. Richardson, M.D.

Abstract

The elderly, aged 65 or older, are more susceptible to illness or injury due to environmental factors, physiologic deterioration and co-morbid disease. Prompt referral of patients with acute decompensation to the Emergency Department promotes resuscitation, rapid evaluation and interventions where appropriate, to improve outcomes. Common life- or limb-threatening situations are reviewed as well as co-morbidities and social issues that may complicate decision making.

Key Words: Geriatric, emergency, emergency department, elder, aged, review.

In the U.S., advances in medicine, including antibiotics, cardiovascular interventions, surgical techniques and lifestyle modifications, have added years to longevity. Multicenter surveys in the 1990s indicated that approximately 15% of all visits to emergency departments (EDs) were made by the elderly. This number is projected to be 25% by the year 2020 as the baby boomers reach senior status (1, 2). By the year 2030, 1 in 5 persons will be older than 65 years. Relative to younger cohorts, elders require more ambulance transport, consume more time and ED resources, and are more likely to have serious disease or injury which requires admission to the hospital. Collaboration between the primary provider and ED physician is essential to identify patient problems amenable to outpatient evaluation as well as to provide early referrals for acute conditions of accident or illness for which rapid referral to the Emergency Department may promote a better outcome.

Resuscitation must always be a priority, with attention given to respiratory and circulatory status. Following stabilization of obvious threats to life or limb, one must establish current deviation from baseline function. Often elders in the ED are too sick, or are unwilling or unable to provide a coherent history, or information on allergies, medications, medical/surgical history, or recent interventions. Fear of loss of independence or memory deficits may make it impossible for them to characterize their baseline level of cognitive and daily functional status. Information from health providers, family, paramedics or old records can provide essential clues to preexisting conditions and rate of decline, which can aid in targeting treatment. Transmittal of advance directives regarding DNR status also prevents the use of unwanted "heroic measures" and promotes respect for patient wishes regarding end-of-life care.

The task of the ED physician, beyond resuscitation, is to quickly sift through available information gained from the history, physical examination, initial imaging or laboratory studies, and then ascertain the likelihood of serious injury or illness.

Psychosocial confounders such as depression, suicide risk, elder abuse and alcoholism weigh heavily in the decision to admit a patient when the conditions are ordinarily amenable to outpatient management. Alcohol abuse has been shown to be an acute factor in up to 14% of elder ED visits (3). Presentations vary from the expected, such as falls and injury, rapid atrial fibrillation, or cardiomyopathy, to vague gastrointestinal complaints, insomnia, and depression. A useful screening device, developed by

---

Clinical Associate Professor of Emergency Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Barbara K. Richardson, M.D., Department of Emergency Medicine, Box 1620, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Material in this article was presented at the Mount Sinai School of Medicine Geriatric Medicine Update and Board Review Course, New York, NY, on October 8, 2001.

This manuscript has been updated as of August 5, 2002.

Ewing, is the CAGE score (4), in which any two positive responses have been shown to have a 70% sensitivity for significant alcohol involvement. CAGE stands for four possible responses to one's alcohol consumption: C (cutting down), A (annoyed about alcohol consumption questions), G (guilty about alcohol consumption) or E (need for an early morning eye opener). Failure to elicit alcohol dependence can lead to misdiagnosis when admitted patients go into withdrawal. Provision of adequate hydration and benzodiazepines to control agitation will reduce morbidity.

Drug-drug or adverse drug reactions (ADRs) account for up to 5% of hospital admissions among the elderly (5). Patients who maintain a list of their current medications can assist physicians in identifying this problem. On average, most elders use more than 4 prescription drugs and 1 or 2 over-the-counter drugs. Nursing home patients receive an average of 7.2 medications at any given time in their stay (6). Polypharmacy must be considered in the differential diagnosis of acute decline in mental status in the elderly. Drugs which are frequently implicated include anticoagulants, sedatives, antihistamines, tricyclic antidepressants and anticholinergics (7).

Major Disease Entities in the Elderly

Altered Mental Status

The differential diagnosis of altered mental status is broad and includes: central nervous system (CNS) bleeds; clots; mass or infection; post-ictal state; all forms of shock, particularly septic and hypovolemic; metabolic disorders, including end-stage dysfunction of any organ; environmental disorders such as hypothermia or heatstroke; and endocrine disorders, including thyroid, diabetes, Addison's, pulmonary embolus, toxins and trauma. Lacking historical or physical clues, the evaluation is extensive and includes a sepsis work-up, CT scanning, toxic and metabolic screens, chest X-ray and cardiac evaluation. It should be noted that in elder patients with extreme agitation lacking a readily reversible cause, small titrated doses of a neuroleptic, haloperidol, are less likely to cause oversedation and disinhibition than a benzodiazepine, such as lorazepam, although both have been used successfully in selected patients (8). The search for cause can thus be facilitated while reducing the chance of injury to the patient or others. If multiple or higher doses are needed, meticulous ongoing attention to airway, arrhythmias and hemodynamic status is required. Hypotension, respiratory depression, and *torsades de pointes*, although rare, can occur.

Delirium

Delirium, which carries a 10–22% risk of in-hospital mortality, is possible in any patient with an acute alteration in mental status who has not had an obvious stroke (9). Although delirium is more common in patients with dementia, one must differentiate delirium from dementia and psychiatric illness, since delirium represents a more acute condition which may have a reversible cause. Delirium can be triggered by abnormalities in vital signs (temperature, blood pressure, pulse, respiratory rate or oxygen saturation), or by infection, myocardial infarction, acute abdomen or trauma. Delusions and hallucinations, often visual, can occur in up to 40% of patients. The Confusion Assessment Method, developed by Inouye, is shown in Table 1 (10); the presence of the first 2 features and one additional feature has a 94% sensitivity, 90% specificity in differentiating delirium from dementia.

TABLE 1
Confusion Assessment Method

1. Acute onset or fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

(Examples: hypervigilant, lethargic, stuporous, comatose)

Reproduced with permission from Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113:941–948 (10).

Gradual and progressive decline in cognitive function is more typical of dementia, of which the most common types are Alzheimer's and vascular dementias. The Folstein Mini-Mental Exam (11), easily administered in the ED, uses a cutoff of 23 or below to separate patients with delirium or dementia from those with other disorders. Comprehensive evaluation of memory decline is beyond the scope of the ED. Admission decisions revolve around discovery of acute illness requiring in-hospital treatment in lieu of clearly unsafe home situations. Finally, formerly independent patients who were recently able to "get up and go," but are now unable to do so, are unlikely to be successfully discharged from the ED (12).

Stroke

Abrupt alteration in speech, vision, motor or sensory function suggests acute stroke, which is defined as the sudden onset of a focal deficit corresponding to a vascular territory. For outpatient providers, use of a simple screen such as the Cincinnati Stroke Scale (13) has a 72% sensitivity if any of three signs are positive: new changes in facial asymmetry enhanced by smiling, upper extremity motor drift with eyes closed when both arms are extended, or change in speech. If time of onset of stroke is known with certainty to be less than 3 hours earlier, the patient with moderate deficit and no contraindication may be eligible for brain salvage via clot dissolution. In such cases, rapid transport to, and notification of, the ED can activate a stroke team composed of the ED staff, neurologist and radiologist. This stoke team can facilitate evaluation and selection of candidates who would benefit from the procedure. Stroke mimics such as hypoglycemia, hypertensive crisis and post-ictal state must be excluded. Patients undergo noncontrast head CT to exclude those who have intracranial hemorrhage. Patients who arrive at the ED within the time frame, have a persistent significant deficit, and lack a preexisting risk of hemorrhage are candidates for tissue plasminogen activator (t-PA). NINDS (14) data demonstrated a 30% reduction in major disability from stroke for t-PA recipients with moderate deficit ischemic stroke under ideal circumstances.

Acute Coronary Syndromes

Acute coronary syndromes are represented in disproportionately high frequency and remain the leading cause of death among the elderly. As with strokes, early recognition and referral to the ED holds the key to reduction in disability and the number of deaths. All patients with potential ischemia by history should have an immediate ECG to assess for ST segment elevation myocardial infarction (STEMI), and prompt initiation of reperfusion strategy, which has been shown to reduce LV dysfunction and mortality (15). All patients with acute myocardial infarction (MI) may benefit from aspirin, beta-blockers, oxygen, heparin, and angiotensin-converting enzyme inhibitors unless there are specific contraindications to their use. If pain persists, the use of nitrates may be appropriate (16). Reperfusion strategies may include percutaneous transluminal coronary angioplasty (PTCA) if available in less than 120 minutes from time of ED entry, or fibrinolysis in patients without bleeding contraindication who present in less than 6–12 hours of onset of symptoms. Many randomized controlled trials in acute MI patients have excluded the elderly. Although retrospective in nature, a recent multicenter review showed a positive benefit of fibrinolysis for those 65–75 years of age but a reverse effect on mortality for those over 75, due to severe hemorrhage (17).

Clearly, aggressive reperfusion strategies are appropriate for physiologically younger candidates. PTCA, when readily available in high-volume centers, achieves statistically better outcomes (18).

As for symptoms, patients over 85 years complain more often of dyspnea than of chest pressure (19). Other nonspecific symptoms include altered mental status, malaise, "flu," diaphoresis, exhaustion and sudden inability to ambulate. Patients with symptoms and nondiagnostic ECGs should have serial cardiograms, cardiac markers (creatine kinase-myocardial band [CK-MB] and troponin), and a period of monitoring of 6–24 hours, depending upon onset of pain. Troponin, which remains elevated for 5–10 days beyond CK-MB, is useful in identifying patients with acute MI, or those at high risk for adverse cardiac event who present after 24 hours of onset (20). Patients with true unstable angina, with a history and dynamic ST segment ECG changes, or elevated troponin appear to benefit from one of the parenteral IIb/IIIa glycoprotein inhibitors and reduced-dose heparin if PTCA is planned within 12–24 hours. No significant increase in intracranial hemorrhage was seen, although there was an increase in low platelets and in bleeding at catheter sites (21). Patients who might be candidates for interventional treatments and who have not developed an MI during the monitoring period can be further risk stratified using stress testing or cardiac catheterization.

Pulmonary Embolus and Aortic Dissection

Other critical diagnoses to consider when acute chest pain and/or shortness of breath present include pulmonary embolus and aortic dissection. Pulmonary embolus is more likely in patients with history of thromboembolism, stasis/immobility, hypercoagulable state or endovascular injury. Selection of the initial diagnostic test, such as CT angiogram, ventilation perfusion scan, or transesophageal echocardiogram, depends upon the stability of the patient and the available expertise within the institution. For pretest moderate-to-high likelihood of pulmonary embolus, anticoagulation with unfractionated or low-molecular-weight heparin is instituted in nonbleeders before diagnostic testing.

While potentially lifesaving for pulmonary embolus, anticoagulation would be life-threatening for cases of aortic dissection. Dissection, suspected in stable patients with severe and/or migrating chest pain, can often be diagnosed via CT angiogram. Unstable patients need analgesics and rapid lowering of severe hypertension via beta-blocker and sodium nitroprusside, as well as prompt cardiothoracic consultation. Beta-blockers, due to significant unopposed alpha vasoconstriction, cannot be used in patients whose chest pain is precipitated by cocaine abuse. Fortunately, this is a rare etiology among elderly patients with chest pain.

Infections

Infections represent another common cause of rapid functional decline among the elderly. Although presentation of infection may be atypical in the elderly due to absence of fever or localizing symptoms and signs, this has more to do with physiologic status than with exact chronologic age (22). Rectal temperatures should be obtained when fever is uncertain. Bacterial etiology is much more likely in febrile elders than are viral infections, which are so common in younger patients (23). Previously healthy, vigorous elders become infected with the same community-acquired organisms as do younger cohorts. Debilitated elders present more of a challenge in detection of infection and decision making about antibiotic coverage as a result of reduced immunocompetence, breakdown of skin barriers, indwelling tubes and prostheses, co-morbid diseases and recent antibiotic exposure, which may select for resistant pathogens. Respiratory infections account for approximately one-third, whereas urinary tract infections and sepsis each account for one-fifth of infections in elders (24). Abdominal infections, septic arthritis, endocarditis and meningitis, while less common, are not rare.

Pneumonia. Pneumonia is common in the elderly, in part because of their decreased ability to cough, diminished vital capacity and mucociliary clearance, and the increased potential for aspiration. It carries an inpatient mortality of 14–32% (25). Common organisms include pneumococcus and staphylococcus, but gram negatives and tuberculosis can occur, particularly in patients from nursing homes. Hospital-acquired pneumonia is more likely to include gram negatives such as *Klebsiella* or *Pseudomonas* (24). Assessment of adequacy of oxygenation via pulse oximetry, chest X-ray to confirm diagnosis and identify high-risk features, blood cultures before antibiotics in patients being admitted, and early administration of antibiotics have a favorable effect on outcome (26, 27). Suggested empiric antibiotics include an extended spectrum fluoroquinolone or third-generation cephalosporin and a macrolide (28). Most likely to require ICU care are patients with shock, hypoxemia, or increased work of breathing. Respiratory isolation is required for elders suspected of tuberculosis by indolent history or apical, miliary or cavitary infiltrates on X-ray. EDs can also play a valuable role by providing influenza vaccination as a preventative measure for elders who fail to get regular medical care (29).

Urinary Tract Infections. Urinary incontinence, pelvic floor relaxation, and prostatic obstruction, as well as over-reliance on indwelling urinary catheters, are believed to be responsible for the significant incidence of urinary tract infections among the elderly (30). Patients with new urinary symptoms and bacteriuria or pyuria require treatment. Patients suspected of having urosepsis need rapid administration of antibiotics after cultures are taken. Foley catheters, although implicated in etiology, are needed for urinary retention. Imaging studies, ultrasound or contrast CT may be needed if proximal obstruction or abscess is suspected. Antibiotics pending cultures, particularly in institutionalized patients, should cover resistant gram negative bacilli such as *Klebsiella*, *Enterococcus* and *Pseudomonas*. Local resistance patterns should be reviewed. A quinolone, beta lactam inhibitor, piperacillin-tazobactam or ampicillin and gentamicin are possible empiric choices (31).

Soft Tissue Infections. Serious soft tissue infections are more common in debilitated elders. Emergent surgical consultation should be sought for any soft tissue infection associated with severe pain, especially when the infection advances rapidly despite antibiotic therapy or has any black, necrotic areas. Compartment syndromes, necrotizing fasciitis and perineal involvement (Fournier's gangrene) may have poor outcomes despite prompt, meticulous surgical attention.

Acute Abdominal Pain

Early collaboration with surgical colleagues is also essential in evaluation of selected cases of acute abdominal pain, since up to 40% of elderly patients presenting with acute abdominal pain require surgery (32). Delay in diagnosis is common, due to coexisting chronic conditions, fear of cancer, minimization by patients and their providers, dementia, and limited access to care. Red flags suggesting serious surgical pathology include acute onset of pain which awakens the patient from sleep, is continuous or steadily worsening; pain before onset of vomiting seen in small bowel obstruction or cholecystitis; localization of pain; peritoneal signs; bloody effluents; or frank shock (33).

Data from de Dombal (34) and modified from Telfer et al. (35), shown in Table 2, from a multinational series of patients spanning nearly 20 years in the late 1960s and 1970s, suggests important differences in etiologies when stratified by age. We anticipate that results of multicenter U.S.-based studies now in progress will clarify the impact of advances in imaging and surgical techniques on diagnosis and outcome.

Abdominal pain, representing 5 – 10% of ED visits, is the most time-consuming complaint in the ED, because the approach must focus on excluding worst-case scenarios. However, in contrast to the situation with younger patients, the diagnosis can be made for approximately 75% of older patients (36). Although cholecystitis is the most common reason for abdominal surgery in the elderly, appendicitis and small bowel obstruction are the most frequent causes for elderly patients to be discharged inappropriately from the ED (37, 38). Inferior wall MI and lower lobe pneumonia should be considered in older patients who complain of epigastric pain and who appear acutely ill; other possible diagnoses are impending abdominal catastrophe, including dissection, leaking abdominal aortic aneurysm, volvulus or perforation.

TABLE 2

Acute Abdominal Pain Stratified by Age (34, 35)

Diagnosis	≥ 50 Years n=2406	<50 Years n=6317
Biliary tract disease	21%	6%
Undifferentiated abdominal pain	16%	40%
Appendicitis	15%	32%
Bowel obstruction	12%	2%
Pancreatitis	7%	2%
Diverticular disease	6%	<0.1%
Cancer	4%	<0.1%
Hernia	3%	<0.1%
Vascular	2%	<0.1%
Gynecologic disease	<0.1%	4%

Modified from Telfer S, Fenyo G, Holt PR, de Dombal FT. Acute abdominal pain in patients over 50 years of age. Scand J Gastroenterol Suppl 1988; 144:47 – 50, www.tandf.no/gastro, by permission of Taylor and Francis AS (35).

The pathophysiology of aging involves thinning of the abdominal musculature, shrinking of omentum and diminished blood supply. Pain, therefore, may not be well localized; guarding and rebound may be delayed or absent while irreversible necrosis of the bowel is progressing (39).

Priorities in care include intravenous rehydration, nasogastric decompression if obstruction is likely, analgesia, and empiric antibiotics after cultures if there are signs of peritonitis. "Nondiagnostic" abdomens in patients with continuing complaints must be re-examined regularly by a skilled examiner. Imaging techniques, especially contrast CT scans, should be used more liberally for stable elders in whom urgent surgery is not contemplated or for whom the etiology of pain is obscure. Admission may be necessary in 50 – 60% of cases (40). Patients well enough to be discharged following a full examination should be expedited in reappraisal within 6 – 8 hours of discharge if symptoms recur or progress.

Abdominal aortic aneurysm (AAA) and acute mesenteric ischemia are associated with the highest mortality involving abdominal complaints, in excess of 70%, even when the diagnosis is made promptly. Vasculopathy elsewhere in the arterial tree and advancing age are associated risk factors. Consideration of leaking AAA is mandatory in any elder presenting with back pain, abdominal pain, syncope, hypotension, or "renal colic" (41). Identifying a midline laterally pulsatile mass is suggestive, but a technically adequate bedside ultrasound is 100% sensitive in demonstrating the presence of AAA (but not in demonstrating that it is leaking). Unstable patients need to be prepared for the operating room; stable patients can deteriorate abruptly, so that immediate vascular consultation is needed to plan further diagnostic imaging and surgical approach. In less symptomatic patients with well-defined anatomy and significant intraoperative risks, endovascular stenting has been employed with some success (42).

Acute mesenteric ischemia may be due to arterial embolism (65%), nonobstructive low flow (20%) or venous obstruction from hypercoagulable states (15%) (43). Patients with advanced congestive heart failure, recent MI or atrial fibrillation are at highest risk. Pain is often poorly localized, intermittent and sometimes resistant to narcotic administration. A benign abdominal examination early requires frequent re-examination by the physician and surgical consultation if mesenteric ischemia is suspected. Suggestive laboratory results such as marked leukocytosis, lactic acidosis and guaiac-positive stools may be late findings (44). Plain films have value in excluding other diagnoses such as free air or obstruction; the classic "thumb printing" due to submucosal edema or hemorrhage in intestinal ischemia is uncommon and usually signifies infarction. These critically ill patients require aggressive attention to volume status, oxygen-carrying capacity, management of congestive heart failure, and broad spectrum antibiotics. Stability of the patient, pretest likelihood and institutional availability and expertise will determine whether CT angiogram, selective angiogram or magnetic resonance angiogram (MRA) is performed next for more definitive diagnosis (45). The traditional selective angiography defines the anatomy of the obstruction and guides the surgeon in decisions regarding intra-arterial vasodilators, fibrinolysis, embolectomy, stent revascularization or bowel resection (46). Ongoing anticoagulation is always indicated for mesenteric venous thrombosis.

Colonic ischemia differs from mesenteric ischemia in that it is more common; may be associated in 10% of cases with local obstruction such as cancer, stricture, impaction or diverticulosis; can be associated with blood in stool; and presents with more gradual, milder pain and in patients who appear to be less ill. Since the differential includes inflammatory bowel and infectious diarrhea, stool cultures are obtained. Colonoscopy or gentle barium enema within 48 hours completes the work-up (47). Management includes fluids, antibiotics and correction of any cardiac issues. Most cases resolve uneventfully.

Acute cholecystitis is the most common cause of acute abdomen in the elderly. Although classic vomiting, fever and leukocytosis may not be present in up to half of cases, this entity should be suspected in patients with right upper quadrant tenderness or fullness (48). Bedside biliary ultrasound may demonstrate a sonographic Murphy's sign and the presence of stones. Uncertain cases may require a functional study such as an hepato-iminodiacetic acid (HIDA) scan. Emphysematous or gangrenous cholecystitis, seen in elder diabetics, requires immediate decompression. Management of acute cholecystitis includes parenteral hydration, analgesia and antibiotics which include anaerobic and gram negative coverage, and eventual cholecystectomy.

Small bowel obstruction may be caused by adhesions, hernias or intussusception, in descending order. Large bowel obstructions arise more often from neoplasm or volvulus. In one study, gallstone ileus accounted for 35% of nonstrangulated small bowel obstructions (49). Differential air fluid levels on upright abdominal films suggest presence but not location of obstruction. Contrast CT has been used with success to define etiology and location of obstruction (50). Treatment includes rehydration, antibiotics, nasogastric decompression if vomiting is prominent, and surgical consultation. Parkinson's patients are at high risk for volvulus, although they may also have the more benign pseudo-obstruction seen in chronic constipation. Sigmoid, versus cecal or gastric volvulus, has a more gradual onset in patients with a longstanding history of constipation. As the twisted bowel loop grows ischemic and obstructed, severe colic ensues, with a markedly tender, distended abdomen. Obstructive series show dramatic dilatation, sometimes with the characteristic "bent inner tube" appearance. Treatment of sigmoid volvulus in a stable patient is colonoscopic decompression followed by surgery; less common cecal and gastric volvulus require immediate surgery.

Another entity in which the obstructive series may suggest the diagnosis is **perforated peptic ulcer**. Vomiting and a history of pain are not always present. The diagnosis can be missed because patients remain supine for chest and abdominal films. Free air, not always present on plain films, is readily apparent on abdominal CT or repeat upright plain films following the nasogastric tube insufflation of air into the stomach (51).

Appendicitis, present in 15% of elders presenting to the ED with acute abdominal pain, is most likely to perforate in the very young and the very old because of delay in diagnosis (52). Classic findings of rapid migration of pain to the RLQ and anorexia may be absent (35). Leukocytosis is nonspecific and, when lacking, confers a false sense of security. Mild pyuria can occur due to ureteral proximity to the inflamed appendix (53). RLQ focal tenderness is ominous and should prompt immediate surgical consultation. Equivocal cases of appendicitis or diverticulitis may be diagnosed by abnormalities on rectal contrast CT. Findings include a collection, or fat stranding suggesting inflammation, and absence of normal appendix (54).

Trauma

Trauma is the fifth leading cause of death among the elderly and represents 25% of trauma fatalities and trauma costs (55, 56). The mechanism of injury differs between younger and older patients. Falls are most common, followed by motor vehicle collisions (MVC) and pedestrian-MVC, followed by stab wounds and gunshot wounds.

In addition to assessing the extent of the injuries, it is critical to evaluate the possibility of a precipitating event such as syncope, situational confusion, gait disturbance or metabolic abnormalities. Failure to appreciate transient ischemic attack, acute MI, cardiac dysrhythmia, orthostatic hypotension, pulmonary embolus, hypoglycemia, stroke, gastrointestinal hemorrhage, shock, adverse drug reaction, assault, elder abuse or other confounder will substantially increase mortality (57). Elders with trauma who cannot recall the event should be admitted for further evaluation.

Factors which will affect response to injury and outcome in elder trauma include: head injury, pedestrian vs. auto, multiple long-bone fractures, acidosis ($pH < 7.35$) and initial systolic blood pressure ($SBP) < 130$ (58). Close collaboration between emergency physicians, surgeons and intensivists is required to facilitate care and enhance outcome. Typical parameters for monitoring response to resuscitation in younger cohorts, such as blood pressure, pulse and urine output, are less sensitive indicators in the elderly. Aggressive assessment of extent of injury, attention to the need for ventilatory support, resuscitation with invasive hemodynamic monitoring, early transfusion, use of inotropes, and rapid provision of intensive care (within 2.2 hours) in multiply injured elder patients improved survival from 7% to 53%, according to Scalea (59).

Physiological alterations with age and their effects on injury and resuscitation are summarized in Table 3 (60–66).

Subdural hematoma, brain contusion and traumatic subarachnoid hemorrhage are more frequent than epidural hematomas in elderly pa-

TABLE 3

Age-Related Changes and Trauma Complications

System	Alteration in Age	Relevance in Trauma
Cardiac (61)	Decreased cardiac output	Congestive heart failure
	Decreased LV function, amyloid	
	Beta or calcium channel blockers	Syncope, relative Bradycardia in shock
	Dysautonomia	Hypovolemia
	Coronary artery disease	Ischemia
	Cardiac dysrhythmias	
	Obstructive valvular disease	
	Antihypertensives, diuretics	Hypokalemia
Pulmonary (62)	Emphysema	Hypoxia
	Decreased functional residual volume	ARDS
	Decreased chest wall compliance	Rib fractures Pneumonia
Renal (63)	Decreased creatinine clearance	Acute tubular necrosis
	Decreased concentrating ability	Contrast, drug toxicity
Neuro (64)	Adherent dura, cortical atrophy	Acute/chronic subdural
	Decreased hearing, vision, increased time to react	Falls, MVC
	Vertigo	Falls
	Cognitive impairment	Falls, MVC, elder abuse
Hematologic (65)	Anemia	Ischemia, hypoxia
	Anticoagulation	Bleeding, especially CNS
Skeletal (66)	Osteoporosis	C1–C3 fractures Wrist, humerus, hip, vertebral, pelvic, skull fractures
	Limited mobility	Thromboembolic disease Skin breakdown, decubiti

ARDS = adult respiratory distress syndrome
MVC = motor vehicle collision
CNS = central nervous system
(In addition to references 61–66, this table is also based on data found in reference 60.)

tients with head trauma (67). The main symptom of acute subdural hematoma is dramatic alteration in mental status; chronic subdurals more often present as subtle personality or cognitive deficits. Noncontrast head CT readily differentiates between acute subdural and subarachnoid hemorrhage. Contrast head CT may be needed for subacute symptoms of more than one-week duration as blood becomes isodense. After stabilization of airway and circulation, liberal use of head CT is advised for all elders with trauma and new focal deficit, alteration in mental status, loss of consciousness, excessive anticoagulation, dementia or intoxication. Similarly, difficulties excluding cervical spine fracture with plain films may be resolved with CT if there is insufficient visualization of all 7 vertebrae or if this is significant degenerative disease. Since the cervical spinal canal may become stenotic from degenerative processes, patients should be closely questioned regarding tingling or burning hands and upper extremity over lower extremity weakness, as seen in central cord syndrome, a subtle but important spinal cord injury without vertebral fracture.

The low velocity of injuries in falls by elders, and seatbelt injuries, tend to select for rib fractures over aortic disruption or pulmonary contusion; nonetheless, multiple fractures can precipitate adult respiratory distress syndrome (ARDS) and require meticulous ICU care or admission for pain management (68). Abdominal injuries include contusions of kidney, liver, spleen and small bowel. In stable patients, contrast abdominal CT for retroperitoneal and solid organ injury, or bedside ultrasound over peritoneal lavage for less stable patients, has been successfully used to identify the need for surgical intervention (69). Mortality remains high.

Extremity Fractures

Extremity fractures due to skeletal fragility are the most common injuries in elder falls and MVCs. The patient may not always guide the examiner to the injured area, so a complete examination of all limbs is needed, looking for deformity, tenderness, crepitance, edema, ecchymosis, and loss of function and distal neurovascular integrity. Although isolated upper extremity fractures are rarely life threatening, impaired mobility of the dominant hand, titration of pain medication and rehabilitation, or concerns of possible elder abuse or neglect, may prompt an admission. Fifty percent of upper extremity injuries are distal radius fractures, followed by humeral fractures and elbow fractures/dislocations (70). In the lower extremities, pelvic rami fractures are more common, but hip fractures are the most frequent indication for admission. If plain films are negative but clinical suspicion high, MRI or bone scan may be needed to delineate occult fracture and avoid displacement and neurovascular injury. Mortality from hip fractures within the year following the event can be as high as 30% (71). Hip dislocations in previously replaced joints, as well as fractures of the tibial plateau and patellar and lateral malleolus are also quite common. Promotion of early ambulation through prompt surgery for hip and some knee fractures, or immobilization and early rehabilitation for ankle fractures, may prevent secondary complications of deconditioning, skin breakdown and deep vein thrombosis.

Burns and Wounds

Tetanus immunization update and meticulous wound care are necessary to prevent morbidity in burns, lacerations and breakdown of the skin. Mortality in burns is a function of total body surface area involved with second and third degree burns, presence of inhalation injury and physiologic age. Fifty percent mortality is estimated for patients over 60 with 10–14% total body surface area burned. Referral to a burn center provides greater likelihood of early grafting for return of function and decrease in infectious complications (72).

Analgesia

Attention to adequate analgesia is paramount in the management of elders with serious illness or injury (73). Patients with dementia or aphasia should not be considered incapable of experiencing pain, even though they may be unable to complain. Titration of parenteral opiates is appropriate for patients in severe pain. Nonoperative patients with mild-to-moderate pain syndromes can be managed with acetaminophen with or without codeine. Use of opiates will also require addition of a bowel regimen to prevent constipation. Selective COX-2 inhibitors appear to have less gastrointestinal toxicity than other nonsteroidals but should generally be avoided in patients with a history of bleeding, active peptic ulcer or renal insufficiency (74).

Summary

This article has sought to review some of the common and potentially life-threatening emergencies of the elderly. Early intervention in acute accident and illness requires prompt referral to the Emergency Department. Provision of key historical information by phone or fax or from the patient or caregiver is of inestimable value in focusing ED efforts and avoiding disaster or loss of patient autonomy. Work-ups are necessarily more comprehensive than those required for younger patients. Surgical consultation in cases of trauma and abdominal pain is often indicated. Rapid referral, diagnosis and treatment may reduce morbidity in cases of stroke, acute coronary syndrome, infection, abdominal crisis and injury. Precipitating events, co-morbid diseases, medications, social support systems and need for analgesia must be carefully considered. Admission for observation may be needed when serious illness or injury is suspected and cannot be excluded. Availability of high-quality emergency care and close collaboration with regular providers is essential to optimal outcomes from sudden decompensation in the elderly. When mortality is likely, given extent of injury, burn or irreversible underlying condition, provision of palliative care is paramount.

References

1. Strange GR, Chen EH. Use of emergency departments by elder patients: Five year follow up study. Acad Emerg Med 1998; 5(12):1157–1162.
2. McCaig LF, Ly N. National hospital ambulatory medical care survey: 2000 emergency department survey. Advance data from Vital and Health Statistics. 4/22/02; 326; www.cdc.gov/nchs/ad326.pdf.
3. Adams WL, Magruder-Habib K, Trued S, Broom HL. Alcohol abuse in the elderly emergency department patients. J Am Geriatr Soc 1992; 40:1236–1240.
4. Buchsbaum DG, Buchanan BA, Welsh J, et al. Screening for drinking in the elderly using the CAGE questionnaire. J Am Geriatr Soc 1992; 40:662–665.
5. Beers MH, Storrie M, Lee G. Potential adverse drug interactions in the emergency room. Ann Intern Med 1990; 112:61–64.
6. http://www.mayo.edu/geriatrics-rst/NH.RTF.html accessed 6/30/02.
7. Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. JAMA 1994; 272:292–296.
8. Pousada L. Common neurologic emergencies in the elderly patient. Clin Geriatr Med 1993; 9:577–590.
9. Lewis LM, Miller DK, Morley JE, et al. Unrecognized delirium in ED geriatric patients. Am J Emerg Med 1995; 13: 142–145.
10. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113:941–948.
11. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psych Res 1975; 12:189–198.
12. Bernstein F. Functional assessment, mental status and case finding. In: Sanders AB, editor. Emergency care of the elder person. St. Louis (MO): Beverly Cracom; 1996. pp. 97–115.
13. Kothari RU, Pancioli A, et al. Cincinnati Pre-hospital Stroke Scale: reproducibility and validity. Ann Emerg Med 1999; 33:373–378.
14. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rtT-PA Stroke Study Group. N Engl J Med 1995; 333: 1581–1587.
15. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb)Angioplasty Substudy Investigators. A clinical trial comparing coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997; 336:1621–1628.
16. Friesinger GC, editor. Cardiovascular disease in the elderly in cardiology clinics. Philadelphia (PA): WB Saunders; 1999.
17. Thiemann DR, Coresh J, Schulman SP, et al. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation 2000; 101:2239–2246.
18. Cucherat M, Bonnefoy E, Tremeau G. Primary angioplasty versus intravenous thrombolysis for acute myocardial infarction (Cochrane Review). http://www.cochrane.org/cochrane/revabstr/ab001560.htm.
19. Solomon CG, Lee TH, Cook EF, et al. Comparison of clinical presentation of acute myocardial infarction in patients older than 65 years of age to younger patients: the Multicenter Chest Pain Study experience. Am J Cardiol 1989; 63: 772–776.
20. Tanasijevic MJ, Cannon CP, Antman EM. The role of cardiac troponin I (cTnI) in risk stratification of patients with unstable coronary artery disease. Clin Cardiol 1999; 22:13–16.
21. Bhatt DL, Topol EG. Current role of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. JAMA 2000; 284:1549–1558.
22. Marco CA, Schoenfeld CN, Hansen KN, et al. Fever in geriatric emergency department patients: clinical features associated with serious illness. Ann Emerg Med 1995; 26:18–24.
23. Wasserman M, Levinstein M, Keller E, Lee S. Utility of fever, white blood cells, and differential count in predicting bacterial infection in the elderly. J Am Geriatr Soc 1989; 37:537–543.
24. Stalam M, Kaye D. Antibiotic agents in the elderly. Infect Dis Clin North Am 2000; 14(2):357–369.
25. Marrie TJ, Blanchard W. A Comparison of nursing home acquired pneumonia patients with patients with community acquired pneumonia and nursing home patients without pneumonia. J Am Geriatr Soc 1997; 45:50–55.
26. Meehan TP, Fine MJ, Krumholtz HM, et al. Quality of care, process and outcomes in elderly patients with pneumonia. JAMA 1997; 278:2080–2084.
27. Gleason PP, Meehan TP, Fine JM, et al. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 1999; 159:2562–2572.
28. Bartlett JG. Update in infectious diseases. Ann Intern Med 2000; 133:285–292.
29. Wrenn K, Zeldin M, Miller O. Influenza and pneumococcal vaccination in the emergency department: is it feasible? J Gen Intern Med 1994; 9:245–224.
30. Evans R. Infections in emergency care of the elder person. In: Sanders AB, editor. St Louis: Beverly Cracom; 1996. p. 253.

31. Nicolle LE. Urinary tract infections in the elderly. In: Hazzard, WR. Blass JP, Ettinger WH, et al., editors. Principles of geriatric medicine and gerontology. New York: McGraw-Hill; 1999. pp. 823–834.
32. Brewer BJ, Golden GT, Hitch DC, Rudlof LE. Abdominal pain: an analysis of 1000 consecutive cases in a university hospital emergency room. Am J Surg 1976; 131:219–223.
33. Silen W, editor. Cope's early diagnosis of the acute abdomen. 17th ed. New York: Oxford University Press; 1987.
34. de Dombal FT. The OMGE acute abdominal pain survey. Progress report, 1986. Scand J Gastroenterol 1988; 144: 35–42.
35. Telfer S, Fenyo G, Holt PR, de Dombal FT. Acute abdominal pain in patients over 50 years of age. Scand J Gastroenterol Suppl 1988; 144:47–50.
36. Bugliosi TF, Meloy TD, Vukov LF. Acute abdominal pain in the elderly. Ann Emerg Med 1990; 19:1383–1386.
37. Fenyo, G. Acute abdominal pain in the elderly: experience from two series in Stockholm. Am J Surg 1982; 143:751–754.
38. Horattas MC, Guyton DP, Wu D. A reappraisal of appendicitis in the elderly. Am J Surg 1990; 160:291–293.
39. Phillips SL, Burns GP. Acute abdominal disease in the aged. Med Clin N Am 1988; 72:1213–1224.
40. Marco CA, Schoenfeld CN, Keyl PM, et al. Abdominal pain in geriatric emergency patients: variables associated with adverse outcomes. Acad Emerg Med 1998; 5:1163–1168.
41. Marston WA, Ahlquist R, Johnson G, Jr., Meyer AA. Misdiagnosis of ruptured abdominal aortic aneurysm. J Vasc Surg 1992; 16:17–22.
42. Zarins CK, White RA, Schwarten D, et al. AneuRx stent graft vs. open surgical repair of abdominal aortic aneurysm: multicenter prospective clinical trial. J Vasc Surg 1999; 29: 292–305.
43. Stoney RJ, Cunningham CJ. Acute mesenteric ischemia. Surgery 1993; 114:489–490.
44. Lange H. Jackel R. Usefulness of the plasma lactate concentration in the diagnosis of acute abdominal disease. Eur J Surg 1994; 160:381–384.
45. Rha SE, Ha HK, Lee SH, et al. CT and MRI imaging findings of bowel ischemia from various primary causes. Radiographics 2000; 20: 29-42.
46. Park WM, Cherry KJ, Jr., Chua HK, et al. Current results of open revascularization for chronic mesenteric ischemia: a standard for comparison. J Vasc Surg 2002; 35:853–859.
47. Greenwald DA, Brandt L, Remius JF. Ischemic bowel disease in the elderly. Gastroenterol Clin North Am 2001; 30(2): 445–473.
48. Glenn F. Surgical management of acute cholecystitis in patients 65 years of age and older. Ann Surg 1981; 193:56–59.
49. Reisner RM, Cohen JR. Gallstone ileus: a review of 1001 cases. Am Surg 1994; 60:441–446.
50. Suri S, Gupta S, Sudhaker PJ, et al.. Comparative evaluation of plain films, ultrasound and CT in the diagnosis of intestinal obstruction. Acta Radiol 1999; 40:422–428.
51. Maull Kl, Reath DB. Pneumogastrography in the diagnosis of perforated peptic ulcer. Am J Surg 1984; 148:340–345.
52. Sanson TG, O'Keefe KP. Evaluation of abdominal pain In the elderly. Emerg Med Clin North Am 1996; 14(3):615–27.
53. Elangovan S. Clinical laboratory findings in acute appendicitis in the elderly. J Am Board Fam Pract 1996; 9:75–78.
54. Rao PM , Rhea JT, Novelline RA, et al. Helical CT combined with contrast material administered only through the colon for imaging of suspected appendicitis. AJR Am J Roentgenol 1997; 169:1275–1280.
55. Hoyert DL, Kochanek KD, Murphy SL. Deaths: final data for 1997. National Vital Statistics Reports from the Centers for Disease Control and Prevention; http://www.cdc.gov/nchswww/data/nvs_19.pdf.
56. Schwab CW, Kauder DW. Trauma in the geriatric patient. Arch Surg 1992; 127:701–706.
57. Zietlow SP, Capizzi PJ, Bannon MP, Farnell MB. Multisystem geriatric trauma. J Trauma 1994; 37:985–988.
58. Morris JA, MacKenzie EJ, Edelstein SL. The effect of preexisting conditions on the mortality in trauma patients. JAMA 1990; 263:1942–1946.
59. Scalea TM, Simon HM, Duncan AO, et al. Geriatric blunt multiple trauma: improved survival with early invasive monitoring. J Trauma 1990; 30:129–134.
60. Schwab CW, Shapiro MB, Kauder DR. Geriatric trauma. Patterns, care and outcomes. In: Mattox KL, Feliciano DV, Moore EE, editors. Trauma. New York; McGraw-Hill; 2000. pp. 1099–1113.
61. Davies MJ, Lye M. Pathology of the aging heart. In: Brocklehurst JC, Tallis RC, et al., editors. Textbook of geriatric medicine and gerontology. Edinburgh: Churchill Livingstone; 1992. pp. 181–185, 188–205.
62. Enright PL. Aging of the respiratory system. In: Hazzard WR, Blass JP, Ettinger WH, et al., editors. Principles of geriatric medicine and gerontology. New York: McGraw Hill; 1999. pp. 721–728.
63. Bartlett RH. Critical care physiology. Boston: Little, Brown; 1996. p. 134.
64. Osler T, Hales K, Baack B, et al. Trauma in the elderly. Am J Surg 1988; 156:537–543.
65. Scalea TM, Simon HM, Duncan AO, et al. Geriatric blunt multiple trauma: improved survival with early invasive monitoring. J Trauma 1990; 30:129–134; discussion 134–136.
66. Riggs BL, Melton LJ III. Involutional osteoporosis. N Engl J Med 1986; 314:1676–1686. Review.
67. Demarest GB, Osler TM, Clevenger FW. Injuries in the elderly: evaluation and initial response. Geriatrics 1990; 45:36–42.
68. Shorr RM, Rodriguez A, Indeck MC, et al. Blunt chest trauma in the elderly. J Trauma 1989; 29:234–237.
69. Tornetta P, Mostafavi H, Riina J, et al. Morbidity and mortality in elderly trauma patients. J Trauma 1999; 46:702–706.
70. Miller MD. Orthopedic trauma in the elderly. Emerg Med Clin North Am 1990; 8:325–339.
71. Keil DP, Eichorn A, Intrator O, et al. The outcomes of patients newly admitted to nursing homes after hip fractures. Am J Public Health 1994; 84:1281–1286.
72. Kara M, Peters WJ, Douglas LG, Morris SF. An early surgical approach to burns in the elderly. J Trauma 1990; 30: 430–432.
73. Jones JS, Johnson K, McNinch M. Age as a risk factor for inadequate emergency department analgesia. Am J Emerg Med 1996; 14:157–160.
74. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDS. JAMA 1999; 282(20):1929–1933.

Stability of Preferences Regarding Life-Sustaining Treatment:

A Two-Year Prospective Study of Nursing Home Residents

ELAINE MCPARLAND, M.D., J.D.[1], ANTONIOS LIKOUREZOS, M.A., M.P.H.[2], EILEEN CHICHIN, PH.D., D.S.W.[2],
TITA CASTOR, M.D.[2], AND BARBARA E.C. PARIS, M.D.[3]

Abstract

Background: The use of advance directives is based on the consensus that physicians should respect preferences expressed by competent patients about future treatments. Patient preferences are, however, subject to change and may be influenced by a number of factors. The purpose of our study was to evaluate the durability over time of decisions made regarding terminal care of mentally intact nursing home patients and the influence of such factors as intervening illness, loss of significant others, and cognitive, emotional and functional decline.

Methods: We undertook a longitudinal prospective cohort study in which 65 mentally competent nursing home patients were interviewed at three intervals (at baseline and after one and two years). For each patient, demographic, medical and socioeconomic data were collected and assessment of mood, function, cognition and preference for life-sustaining therapies (including cardiopulmonary resuscitation and parenteral and enteral nutrition) was obtained.

Results: Preferences regarding cardiopulmonary resuscitation and parenteral and enteral nutrition changed over both the 12- and 24-month study periods. Only degree of change in cognitive status proved to be predictive of changes in decision. Gender, presence or absence of depression, change in level of functional abilities and intercurrent illness or stressor did not influence change regarding life-sustaining therapy.

Conclusions: In light of our findings, we suggest that periodic re-evaluation of these advance directives be performed and that ongoing discussions be initiated with their patients by health care professionals.

Key Words: Advance directives, life-sustaining treatment, stability of decisions.

Introduction

THE USE OF ADVANCE DIRECTIVES has been widely endorsed by legislation and by health care professionals as a way to increase layperson involvement in decisions regarding the use of life-sustaining treatments. However, enthusiasm for these documents must be tempered by the realization that there is a dearth of empirical evidence regarding many of the specific issues surrounding their use. One unresolved issue is the stability, over time, of the decisions expressed in these documents. At present, there are no time constraints placed on the applicability of advance directives once they have been executed. The assumption is made that decisions made at one point in time will continue to reflect a person's preferences in the future. However, this may not be accurate, as clinical and psychological circumstances can change significantly from the time of execution of an advance directive to the moment of treatment choices. Preferences may, in fact, be subject to a variety of influences, including alteration in clinical, functional, cognitive and emotional status.

Advance directives are particularly relevant instruments for specific populations at high risk

---

[1]Mount Sinai School of Medicine, [2]The Jewish Home and Hospital, and [3]Henry L. Schwartz Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY.

This research was supported in part by an American Federation for Aging Research/John A. Hartford Foundation Fellowship, and was conducted at the Jewish Home and Hospital, New York, NY. The results were presented in part at the 12th Annual Meeting of the American Public Health Association in New York, NY, on November 19, 1996 and the Annual Meeting of the American Geriatrics Society in Atlanta, Georgia, on May 10, 1997. The manuscript has been updated as of July 17, 2002.

Address all correspondence to Dr. Paris, Division of Geriatrics, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn, NY 11219.

of morbidity or mortality. Elderly persons, especially those confined to long-term care facilities, are a group for whom life-sustaining treatment decisions carry profound medical and ethical implications. It is for this patient population that clinical status and support systems are frequently tenuous and for whom resolution of specific issues surrounding the use and implementation of these documents is particularly meaningful.

We reviewed 15 articles (1–15) which specifically raised the issue of stability of decisions regarding life-sustaining treatment. The outcome data of these previous studies has, with some exceptions (9–12), supported the assumption that a patient's prior expression of treatment choices accurately represents future choices. However, only one (7) of these previous studies actually assessed this issue among nursing home residents, and none were specifically designed to evaluate the remaining life expectancy of its study population, as was ours. Nursing home residents represent a growing segment of our population, whose singular perspectives on end-of-life care may be influenced by their experiences in a chronic care facility.

This prospective longitudinal study was undertaken to assess the stability of mentally intact nursing home residents' preferences for life-sustaining interventions and to evaluate factors potentially influencing these preferences. The study covered a two-year period, reflecting the average length of stay in a nursing home in the United States today (16). We hypothesized that, in our study sample of nursing home residents: (a) patient preferences would change over time and (b) patient choices would be dependent on changes in life circumstances.

Methods

The study was conducted at the Manhattan (New York) site of the Jewish Home and Hospital ("Home"), a not-for-profit, 514-bed teaching nursing home affiliated with the Department of Geriatrics and Adult Development at the Mount Sinai School of Medicine. The protocol was approved by the Institutional Review Board for the Home. The study utilized the interview method.

The criteria for initial entry into the study were: (a) age over 65, (b) current Folstein Mini-Mental Status Examination (MMSE) (17) score greater than 20, and (c) ability to speak English. We utilized the MMSE because it is an easily reproduced, objective, validated test. The MMSE was originally designed to assess global cognitive status, but it is used most often to screen for dementia and to follow changes in cognition over time. The test was not used in our study to determine capacity, but to exclude residents with severe dementia. Participation was voluntary and informed consent was obtained. The interviews were conducted in person by the same researcher (EM), at the resident's convenience. The setting in which these interviews were conducted provided ample opportunity for directed discussions of these issues, and no time constraints were imposed on the interviewee. Residents were encouraged to discuss the context and application of the interventions, as well as the potential outcomes. The patient interviews ranged from thirty minutes to one hour.

Baseline Interviews

The initial (baseline) interviews were given at the outset of the study (Time 1). The interviews were divided into five sections:

1. **Mental Status** — Mental status was assessed by utilizing the MMSE. The MMSE is a six-category standardized form. Scores range from 0–30, with 0 representing severe cognitive impairment and 30 representing normal cognitive function.

2. **Depression Level** — Mood was assessed by utilizing the Yesavage Geriatric Depression Scale (Short Form) (GDS) (18). The Yesavage Short Form is a validated 15-item questionnaire related to symptoms of depression. Scores range from 0–15, with 0 representing the absence of depressive symptoms and 15 representing severe depression.

3. **Functional Assessment** — The degree of independence in activities of daily living (ADL) was measured by using the modified Barthel Index (BI) (19). This assessment tool measures the individual's performance in 10 ADL functions. The activities evaluated are personal hygiene, bathing, feeding, toileting, stair climbing, dressing, continence, ambulation, and chair/bed transfers. The value assigned to each item is based on the amount of physical assistance required to perform each task. The items are summed to give a score ranging from 10–50, with 10 indicating total dependence and 50 indicating full ability to function independently.

4. **Treatment Preference Questionnaire** — Hypothetical scenarios were utilized to assess resuscitation preferences of the residents.

The scenarios presuppose that the current state of health is good. Residents were presented orally with two possible life-sustaining interventions, cardiopulmonary resuscitation (CPR) and medical hydration and nutrition (MHN), and were asked to indicate their preference in each of the clinical situations. The scenarios, as presented, are as follows:

a) If you stop breathing, you need to be resuscitated in order to stay alive. A technique known as "ventilation" may help you to start breathing again, by having another person breathe directly into your mouth until you start breathing again on your own. If your heart stops, there are several possible ways to try to help your heart start beating again. These include having another person press on your chest with their hands, having an electric shock applied to your chest or having an injection of medicine into your heart or vein. All of these methods are types of cardiopulmonary resuscitation. If the resuscitation is successful, you may be kept alive, but you may suffer partial or severe brain damage. Fewer than 10% of older persons survive to leave the hospital after resuscitation. If the resuscitation is unsuccessful, you will die. Do you think that you would want to be revived by use of these methods if you were unable to breathe or if your heart stopped?

b) If you are unable to eat or drink enough, food may be provided to you through tubes inserted directly into your stomach ("percutaneous endoscopic gastrostomy") or through placement of a tube in your nose ("nasogastric tube"), and/or fluids may be provided to you directly into a vein through a needle ("intravenous line"). This is known as medical hydration and nutrition, and may be continued indefinitely. If you were unable to eat or drink enough on your own, would you want to be artificially hydrated and fed via these methods?

Possible answers to questions regarding the life-sustaining therapies were recorded on a four-point scale: 1 (definitely no), 2 (probably no), 3 (probably yes), and 4 (definitely yes).

5. **Demographic Data** — Demographic data were obtained from the resident's records, if available, or elicited directly from the residents, and included information regarding date of birth, birthplace, religion, race, marital status and number of living children.

Follow-up Interviews

Follow-up interviews were conducted by the same interviewer at 12 months (Time 2) and 24 months (Time 3) following the baseline interview. The same assessments were performed at follow-up as were done at the baseline interview. In addition, participants were queried about intervening illnesses or injuries serious enough to require hospitalization, as well as intercurrent bereavement involving either spouse, children or close friends (hereinafter referred to as "intervening events"). Responses were confirmed by direct review of residents' medical records.

Statistical Analyses

Data storage and analyses were performed with both SPSS Version 9.0 for Windows (20) and SAS Version 6.12 for Windows (21). Responses to the treatment preference questionnaire were coded as a dichotomous response variable ("yes" or "no") reflecting the clinical actions that could be taken for the resident. The participants who answered "don't know" to a particular treatment preference question were excluded from further analysis regarding that question. Level of agreement, controlling for change of residents' preferences between any two interviews, was measured by the *kappa* statistic. The *kappa* statistic is the best measure of agreement or stability of decision making, because it takes into consideration agreement due to chance alone. A *kappa* of 0.70, which indicates a high level of agreement, was chosen as our threshold of stability. Non-parametric bivariate analyses were utilized to assess associations of key variables (GDS, ADL, MMSE and age) with preferences regarding CPR and MHN at baseline. Multivariate logistic regression analysis was applied to assess independent factors potentially associated with changes in these preferences. Independent variables in the analyses included intervening events, age, and degree of change in ADL, GDS and MMSE scores over time. Each variable carried similar weight in the analysis.

Results

Baseline Interview

At baseline, 82 of 512 residents qualified for the study and 65 residents agreed to participate in the initial interview. Fifty-nine (91%) of the residents were Caucasian, with a median age of 85 years (range: 65–102). Medicaid was the prevailing insurance carrier. Additional demographic data are summarized in Table 1. Forty-six residents (70.8%) wanted CPR, 31 (47.7%) desired MHN and 2 (3.1%) answered "don't know" to both questions (Table 2). In the bivariate analyses, levels of depression, functional status, MMSE score and age did not influence responses to the hypothetical scenarios. The median MMSE, GDS, and ADL scores were 27.0 (range: 20.0–30.0), 3.0 (range: 0.0–11.0) and 36.0 (range: 19.0–50.0), respectively.

TABLE 1
Demographic Characteristics at Baseline (n=65)

Characteristic	Number of Patients	%
Age		
Mean	85	
Range	65–102	
Sex		
Male	14	22
Female	51	78
Marital Status		
Ever married	50	77
Never married	15	23
Children		
None	39	60
Have had children	26	40
Religion		
Jewish	40	62
Other	25	38
Race		
White	59	91
Other	6	9

First Follow-up (Time 2)

Ten of the original 65 residents were unable to complete the second set of interviews (one relocated, five died, and four had MMSE scores which dropped below 20). There were no statistically significant demographic differences between the nonparticipants and participants. However, there was a statistical trend toward the nonparticipants being younger in age (p=0.085).

Six (10.9%) residents responded "don't know" to the question regarding CPR and 4 (7.2%) responded "don't know" to the question regarding MHN. Thirty-six residents (73.4%) desired CPR and 23 (45.1%) desired MHN (Table 2). The median MMSE, GDS, and ADL scores were 25.0 (range: 20.0–30.0), 5.0 (range: 2.0–14.0), and 35.0 (range: 19.0–50.0), respectively. Fourteen (25.5%) residents experienced intervening events: 13 (92.9%) were hospitalized and one (7.1%) lost a close friend.

Second Follow-up (Time 3)

Eleven residents were lost to follow-up after 24 months (one relocated, three died, and seven had an MMSE of less than 20). There were no statistically significant demographic differences between the nonparticipants and participants. Two residents (4.5%) responded "don't know" to both questions regarding CPR and MHN. Thirty-one (73.8%) desired CPR and 25 (59.5%) desired MHN (Table 2). The median MMSE, GDS and ADL scores were 24.0 (range: 20.0–30.0), 4.0 (range: 0.0–14.0), and 30.5 (range: 8.0–50.0), respectively. Fourteen (31.8%) had experienced an intervening event since Time 2: twelve (85.7%) had been hospitalized and 2 (14.3%) had lost a close friend.

Stability of Preferences

Resident preferences changed over time, with increasing instability as follow-up times lengthened. A statistically significant number of residents' decisions regarding CPR were unstable over both 12 (Table 3) and 24 (Table 4) months (k=0.415 and 0.306, respectively). At Time 2, 10 of 49 residents had expressed a change in their desire for CPR (Table 3). At Time 3, 11 of 42 residents expressed a change in their decisions made at Time 1. Preferences were more stable regarding MHN between Times 1 and 2 (k=0.687); 43 of 51 residents expressed no change in their preferences (Table 3). Decisions regarding MHN were less stable over the 24-month study period (k=0.469): 11 of the 42 residents changed their minds about this intervention over this time period (Table 4). Overall, a majority of participants consistently desired CPR, whereas somewhat fewer than half desired MHN. However, as time progressed, a greater proportion of individuals favored MHN.

Multivariate Analysis of Factors Potentially Influencing Change in Preference

None of the factors that we examined had a statistically significant relationship to changes

TABLE 2
Percentages and Numbers of Patients Favoring Life-Sustaining Treatments

	Time 1 %	Time 2 %	Time 3 %
Cardiopulmonary Resuscitation (CPR)	46 (70.8)	36 (73.4)	31 (73.8)
Medical Hydration and Nutrition (MHN)	31 (47.7)	23 (45.1)	25 (59.5)

TABLE 3
Stability of Life-Sustaining Preferences from Time 1 to Time 2

	No change %	Yes to No %	No to Yes %	Statistical Measure *kappa*
Cardiopulmonary Resuscitation (CPR) (n=49)	39 (79.6)	6 (12.2)	4 (8.2)	0.415
Medical Hydration and Nutrition (MHN) (n=51)	43 (84.3)	5 (9.8)	3 (5.9)	0.687

TABLE 4
Stability of Life-Sustaining Preferences from Time 1 to Time 3 (n=42)

	No change %	Yes to No %	No to Yes %	Statistical Measure *kappa*
Cardiopulmonary Resuscitation (CPR)	31 (73.8)	7 (16.7)	4 (9.5)	0.306
Medical Hydration and Nutrition (MHN)	31 (73.8)	5 (11.9)	6 (14.3)	0.469

in resident treatment preferences (Tables 5–8). However, certain patterns were apparent. For a change in functional ability (usually a decline), there was a statistical association with a change in MHN preference between baseline and Time 2 (Table 6). Similarly, for a change in cognitive ability (usually a decline), there was an association with a change in CPR preference between baseline and Time 3 (Table 7). Furthermore, although not statistically significant, those residents who had an intervening event were 2.1 times more likely than those who did not, to change their preferences regarding CPR (Table 7).

Discussion

Stability of Treatment Decisions

In our study of nursing home patients, we found decisions regarding desires for CPR and MHN to be unstable over a two-year period. Our results are in contradistinction to most of the prior studies involving treatment preferences, which have found decisions about prospective treatment interventions generally to be stable over time (1–8). In the only previous study involving nursing home patients, Berger and Majerovitz (7) evaluated 37 residents and found preferences for life-sustaining treatment to be stable over a 6-month period.

There have been three small studies that, similar to ours, have found decisional instability in their cohorts' desires for life-sustaining interventions (9–13). The unifying feature in these three studies was that they each involved a severely ill study population, facing the very real and imminent possibility of the need for life-sustaining measures.

There are a number of reasons that may account for our findings. Our study, unlike most of the other studies, involved a population confined to a chronic care facility, comprising acutely ill inpatients and ambulatory outpatients. It may be that, in a long-term care facility, when residents

TABLE 5

Multivariate Analysis: Factors Associated with CPR Preference Change from Time 1 to Time 2

Variable	Adjusted OR	95% Confidence Interval	p value
Intervening Events	0.392	0.058, 2.668	0.339
Amount of Change in ADL	1.062	0.692, 1.629	0.784
Amount of Change in GDS	1.045	0.704, 1.551	0.826
Amount of Change in MMSE	1.256	0.892, 1.769	0.192
Age at Time 1	1.043	0.942, 1.155	0.416

ADL = activities of daily living
GDS = Geriatric Depression Scale
MMSE = Mini-Mental Status Examination

TABLE 6

Multivariate Analysis: Factors Associated with MHN Preference Change from Time 1 to Time 2

Variable	Adjusted OR	95% Confidence Interval	p value
Intervening Events	0.108	0.006, 1.978	0.133
Amount of Change in ADL	1.699	0.968, 2.983	0.065*
Amount of Change in GDS	1.235	0.780, 1.956	0.368
Amount of Change in MMSE	0.649	0.358, 1.174	0.153
Age at Time 1	1.107	0.962, 1.274	0.157

* Statistical trend toward an association
ADL = activities of daily living
GDS = Geriatric Depression Scale
MHN = Medical Hydration and Nutrition
MMSE = Mini-Mental Status Examination

TABLE 7

Multivariate Analysis: Factors Associated with CPR Preference Change from Time 1 to Time 3

Variable	Adjusted OR	95% Confidence Interval	p value
Intervening Events	1.630	0.337, 7.885	0.544
Amount of Change in ADL	1.144	0.973, 1.345	0.102
Amount of Change in GDS	1.099	0.734, 1.647	0.647
Amount of Change in MMSE	1.442	0.952, 2.183	0.084*
Age at Time 1	0.986	0.905, 1.074	0.746

* Statistical trend toward an association
ADL = activities of daily living
GDS = Geriatric Depression Scale
MMSE = Mini-Mental Status Examination

TABLE 8

Multivariate Analysis: Factors Associated with MHN Preference Change from Time 1 to Time 3

Variable	Adjusted OR	95% Confidence Interval	p value
Intervening Events	0.457	0.100, 2.095	0.313
Amount of Change in ADL	1.043	0.897, 1.213	0.584
Amount of Change in GDS	1.153	0.814, 1.634	0.422
Amount of Change in MMSE	1.125	0.778, 1.627	0.530
Age at Time 1	1.046	0.953, 1.148	0.342

ADL = activities of daily living
GDS = Geriatric Depression Scale
MHN = Medical Hydration and Nutrition
MMSE = Mini-Mental Status Examination

are repeatedly exposed to interventions, these interventions become more acceptable to them over time. As people obtain a better understanding of a given procedure, because they have seen it utilized or discussed its use, they may become more comfortable with it. MHN, for example, is an intervention which became increasingly more acceptable to our study participants. Over time, study subjects may have witnessed other residents maintained with this intervention and altered their decisions based on their observations.

It is also possible that the duration of our study, with repeated interviews by the same interviewer, allowed for the development of a relationship between the interviewer and the study participants, which inspired increasingly candid discourse about difficult end-of-life issues. As patients develop more secure relationships with their physicians and other family or professional caregivers, they are more willing to reflect on and discuss these issues.

Factors Associated with Change in Stability

We hypothesized that change in a resident's clinical status, including acute illness, injury or chronic decline (such as worsening functional or cognitive abilities), might affect treatment preferences. The results of our study suggest that, in fact, very few of these factors independently have a significant effect on changes in preferences. However, there was some tendency towards declines in functional and cognitive abilities to affect decisions regarding MHN and CPR, respectively. Such declines may have induced residents to reflect more carefully on their treatment options as they began to perceive themselves as being more and more dependent on their caretakers. The residents may have experienced a stronger desire to more definitively establish preferences for life-sustaining treatment in the face of perceived loss of autonomy. Alternatively, residents' wishes may have changed simply because, over time, they had come to better understand the treatment options.

Limitations

Several limitations of our analyses should be noted. First, the number of residents in our cohort was relatively small, resulting in a low statistical power for detecting significant relationships in the multivariate logistic regression analyses. A larger sample size might have resulted in statistical associations between variables that have borderline statistical significance (i.e., changes in ADL and MMSE scores). In addition, lack of a large sample size necessitated our condensation of treatment responses into a dichotomous scale, which did not allow for specific identification of residents most likely to change their preferences. Residents who answered "probably yes" or "probably no" may be inherently less stable decision-makers than those who give definitive "yes" or "no" answers. Similarly, the exclusion of residents who answered "don't know" from further analyses could have affected our findings. These residents may be more indecisive and may be more influenced by changes in intrinsic and extrinsic circumstances. Also, the small sample size limited our ability to assess factors which influenced a change in a particular direction (i.e., from "no" to "yes" versus "yes" to "no"). Although we were more interested, in this study, in determining which factors influence change, regardless of direction, it would be useful in a larger study to assess the factors that influence change in a particular direction.

Furthermore, our study addressed only two life-sustaining therapies. In reality, in our study population, there is a much broader selection of treatment interventions, with differing levels of risks and benefits.

Conclusions

The results of our study suggest that, at least among elderly nursing home residents confined to a chronic care facility, decisions regarding life-sustaining treatment are subject to change over time. This study, performed over a two-year period, also suggests that such changes may occur at any time during the average remaining lifespan of a nursing home resident. Furthermore, these findings suggest that timely, periodic review of advance directives may be especially important among the chronically ill elderly.

Our findings undermine the current assumption that decisions expressed in these documents are relatively stable and raise the question as to whether these instruments should have constraints placed on them, with either specific time intervals or specific circumstances precipitating re-review. Exactly which circumstances in a patient's life should prompt re-evaluation is controversial. The results of our study suggest that one such circumstance may be a decline in functional status. Our study also indicates that reviewing decisions regarding both emergent and protracted interventions with the patient and family is important. It is also important to ascertain and confirm any changes in those decisions.

Since decisions appear not to be static, directives should be viewed as a means of stimulating patients to contemplate and discuss these issues, and as an invitation for continued dialogue between physician and patient. As more knowledge is disseminated about these issues, continuing modifications should be made to the existing formats of these instruments, so that they facilitate, over time, proper reflection of a patient's wishes concerning various clinical scenarios.

Finally, continuing education should be targeted to nursing home residents, to increase their understanding of the medical interventions, and to health care professionals, to increase their appreciation for both the value and limitations of these directives. However, the ultimate goal — ensuring that these instruments are used effectively — is best accomplished through ongoing dialogue between nursing home residents and their health care providers regarding preferences for life-sustaining care.

Acknowledgments

The authors wish to thank Larry Adel, Diane Meier, M.D., Melissa Hersh and Leigh Rubinstein for their thoughtful and helpful input, and Clyde Schecter, M.D., for his assistance with data analysis.

References

1. Danis M, Garrett J, Harris R, Patrick DL. Stability of choices about life-sustaining treatments. Ann Intern Med 1994; 120:567–573.
2. Emanuel LL, Emanuel EJ, Stoeckle JD, et al. Advance directives. Stability of patient's treatment choices. Arch Intern Med 1994; 154:209–217.
3. Rosenfeld KE, Wenger NS, Phillips RS, et al. Factors associated with change in resuscitation preference of seriously ill patients. The SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Arch Intern Med 1996; 156:1558–1564.
4. Schneiderman LJ, Pearlman RA, Kaplan RM, et al. Relationship of general advance directive instructions to specific life-sustaining treatment preferences in patients with serious illness. Arch Intern Med 1992; 152:2114–2122.
5. Everhart MA, Pearlman RA. Stability of patient preferences regarding life-sustaining treatments. Chest 1990; 97:159–164.
6. Patrick DL, Pearlman RA, Starks HE, et al. Validation of preferences for life-sustaining treatment: implications for advance care planning. Ann Intern Med 1997; 127:509–517.
7. Berger JT, Majerovitz D. Stability of preferences for treatment among nursing home residents. Gerontologist 1998; 38(2):217–223.
8. Cooper-Kazaz R, Friedlander Y, Steinberg A, Sonnenblick M. Longitudinal changes in attitude of offspring concerning life-sustaining measures for their terminally ill parents. J Am Geriatr Soc 1999; 47:1337–1341.
9. Silverstein MD, Stocking CB, Antel JP, et al. Amyotrophic lateral sclerosis and life-sustaining therapy: patients' desires for information, participation in decision making and life-sustaining therapy. Mayo Clin Proc 1991; 66:906–913.
10. Kohut N, Sam M, O'Rourke K, et al. Stability of treatment preferences: although most preferences do not change, most people change some of their preferences. J Clin Ethics 1997; 8:124–135.
11. Chochinov HM, Tataryn D, Clinch JJ, Dudgeon D. Will to live in the terminally ill. Lancet 1999; 354:816–819.
12. Weissman JS, Haas JS, Fowler FJ Jr, et al. The stability of preferences for life-sustaining care among persons with AIDS in the Boston Health Study. Med Decis Making 1999; 19(1):16–26.
13. Carmel S, Mutran EJ. Stability of elderly persons' expressed preferences regarding the use of life-sustaining treatments. Soc Sci Med 1999; 49(3):303–311.
14. Gready RM, Ditto PH, Danks JH, et al. Actual and perceived stability of preferences for life-sustaining treatment. J Clin Ethics 2000; 11(4):334–346.
15. Lockhart LK, Ditto PH, Danks JH, et al. The stability of older adults' judgments of fates better and worse than death. Death Stud 2001; 25(4):299–317.
16. Day AN. Characteristics of Elderly Nursing Home Residents: Data for the 1995 National Nursing Home Survey, Advance Data from Vital and Health Statistics; Number 289, Hyattsville (MD): National Center for Health Statistics, 1997.
17. Folstein MF, Folstein S, McHugh PR. "Mini-mental state." A practical method for grading cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198.
18. Yesavage JA, Brink TL, Rose TL. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982–1983; 17(1):37–49.
19. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol 1989; 42:703–709.
20. SPSS Version 9.0 for Windows. SPSS, Inc. 233 S. Wacker Drive, 11th floor, Chicago, IL 60606.
21. SAS Version 6.12 for Windows. SAS Institute, Inc., SAS Campus Drive, Cary, NC 27513.

Dean's Lecture

Neurotrophins, Growth-Factor-Regulated Genes and the Control of Energy Balance

STEPHEN R. J. SALTON, M.D., PH.D.

Abstract

Neurotrophic growth factors are proteins that control neuronal differentiation and survival, and consequently play important roles in the developing and adult stages of the nervous system. Study of the genes that are regulated by these growth factors has provided insight into the proteins that are critical to the maturation of the nervous system, suggesting that select neurotrophins may play a role in the control of body homeostasis by the brain and peripheral nervous system. Our understanding of the mechanisms of action of neurotrophic growth factors has increased through experimental manipulation of cultured neurons and neuronal cell lines. In particular, the PC12 pheochromocytoma cell line, which displays many properties of adrenal chromaffin cells and undergoes differentiation into sympathetic neuron-like cells when treated with nerve growth factor, has been extensively investigated to identify components of neurotrophin signaling pathways as well as the genes that they regulate. VGF was one of the first neurotrophin-regulated clones identified in NGF-treated PC12 cells. Subsequent studies indicate that the *vgf* gene is regulated *in vivo* in the nervous system by neurotrophins, by electrical activity, in response to injury or seizure, and by feeding and the circadian clock. The *vgf* gene encodes a polypeptide rich in paired basic amino acids; this polypeptide is differentially processed in neuronal and neuroendocrine cells and is released via the regulated secretory pathway. Generation and analysis of knockout mice that fail to synthesize VGF indicate that this protein plays a critical, non-redundant role in the regulation of energy homeostasis, providing a possible link between neurotrophin function in the nervous system and the peripheral control of feeding and metabolic activity. Future experiments should clarify the sites and mechanisms of action of this neurotrophin-regulated neuronal and neuroendocrine protein.

Key Words: Neurotrophin, VGF, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), leptin, hypothalamus, obesity, diabetes, PC12.

Glossary

AGRP	agouti-related polypeptide
Akt	protein kinase B (non-acronymic)
α-MSH	alpha-melanocyte-stimulating hormone
ARC	arcuate nucleus
BDNF	brain-derived neurotrophic factor
B-raf	member of Raf protein family
CART	cocaine- and amphetamine-regulated transcript
CNTF	ciliary neurotrophic factor
CREB	cAMP-response element binding protein
Crk	SH2/SH3 adaptor protein related to the crk oncogene of avian sarcoma virus
C3G	Crk SH3-binding guanine nucleotide-releasing protein
DMV	dorsal motor nucleus of the vagus
DRG	dorsal root ganglion
Gab1	Grb2-associated binder-1
Grb-2	growth factor receptor-bound protein-2
GTG	gold thioglucose
LH	lateral hypothalamus
LHA	lateral hypothalamic area
LTP	long-term potentiation
MAPK	mitogen-activated protein kinase
MC4-R	melanocortin 4 receptor
MEK	mitogen-activated protein kinase
MKP-1	MAP-kinase phosphatase-1
MSG	monosodium glutamate
NfκB	nuclear factor kappa B

Associate Professor of Neurobiology and Geriatrics, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Stephen R. J. Salton, M.D., Ph.D., Fishberg Research Center for Neurobiology, Box 1065, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Adapted from a Dean's Lecture presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on June 6, 2001 and updated as of July 23, 2002.

NGF	nerve growth factor
NGFI-A	NGF Inducible-A
NILE	NGF-Inducible Large External Glycoprotein; L_1 — same protein in human and mice
NPY	neuropeptide Y
NTS	nucleus tractus solitarius
NT-3, NT-4/5, NT-6 and NT-7	neurotrophin-3, -4/5, -6, -7
PC12	pheochromocytoma 12 cell line
PC-1, PC-2	prohormone convertase-1, -2
PCR	polymerase chain reaction
PI-3 K	phosphatidylinositol-3 kinase
PKC	protein kinase C
PLC-γ	phospholipase C gamma
Pomc	pro-opiomelanocortin
PNS	peripheral nervous system
p75NTR	p75 neurotrophin receptor
PVN	paraventricular nucleus
Raf	cellular homologue of murine sarcoma virus 3611 transforming protein
Rap-1	small guanosine triphosphatase (GTPase) of the Ras family
Ras	cellular homologue of murine sarcoma virus transforming protein
Rsk	ribosomal S6 kinase
SHC	Src homology region 2 (SH2)-containing protein
SH-PTP2	Src homology protein tyrosine phosphatase 2
Shp-2	Src homology-2 domain phosphatase
SNT	suc-associated neurotrophin-induced tyrosine-phosphorylated target (suc is yeast p13suc1, which binds the p34cdc2/cdk2 kinase complex)
SOS	son of sevenless; guanine nucleotide exchange factor that activates Ras
Src	cellular homologue of Rous sarcoma virus transforming protein
trkA, trkB and trkC	tropomyosin-related kinase A, B, and C
VGF	protein; a polypeptide secreted by neurons and endocrine cells (non-acronymic)
vgf	gene (when talking about multiple species)
Vgf	mouse gene
VGF	human gene
VMN	ventromedial nucleus

Introduction

Neurotrophins are proteins that are required for neuronal differentiation and survival. Pioneering work by Rita Levi-Montalcini, Stanley Cohen and Viktor Hamburger in the 1950s and early 1960s identified nerve growth factor (NGF) and demonstrated that this protein was required for sympathetic neuron survival both *in vivo* and *in vitro* (1, 2). The later purification and characterization of brain-derived neurotrophic factor (BDNF) (3), a close relative of NGF, allowed the cloning of additional family members based on sequence homology and polymerase chain reaction (PCR) amplification. Six members of the neurotrophin family have been identified in vertebrates, namely NGF, BDNF, NT-3, NT-4/5, NT-6 and NT-7. These polypeptides bind, with different affinities, to the Trk family of receptor tyrosine kinases (TrkA, TrkB and TrkC) and with similar affinities to the p75 neurotrophin receptor (p75NTR), a member of the tumor necrosis factor receptor family, activating complex intracellular signaling pathways, some of which are shown in Fig. 1. Target tissues secrete specific neurotrophins, and these proteins initiate programs of cellular differentiation and support the survival of neuronal subpopulations that express the appropriate receptors and signaling pathways.

Much of our current knowledge of neurotrophin receptor signaling is based on experimental manipulation of PC12 pheochromocytoma cells, a neural-crest-derived line that expresses both TrkA and p75NTR, and responds to NGF by ceasing cell division and differentiating from adrenal chromaffin-like cells (Fig. 2A) into sympathetic neuron-like cells (Fig. 2B) (4). In addition to their use in understanding the transduction of NGF signals via the Akt and PI3 kinases that are critical to cell survival, and the activation of the MAPK and PLC-γ cascades that trigger neural differentiation (5, 6), PC12 cells have been employed to identify the nuclear target genes of these signaling pathways. Synthesis of a number of proteins is rapidly induced in PC12 cells by NGF treatment; these proteins include the transcription factors NGFI-A and Fos, and the dual-specificity tyrosine phosphatase MAPK phosphatase-1 (MKP-1). Long-term NGF treatment leads to increased synthesis of proteins that function in the differentiated neuron, such as the cytoskeletal protein peripherin and the cell adhesion molecule NGF-Inducible Large External Glycoprotein (NILE or L_1).

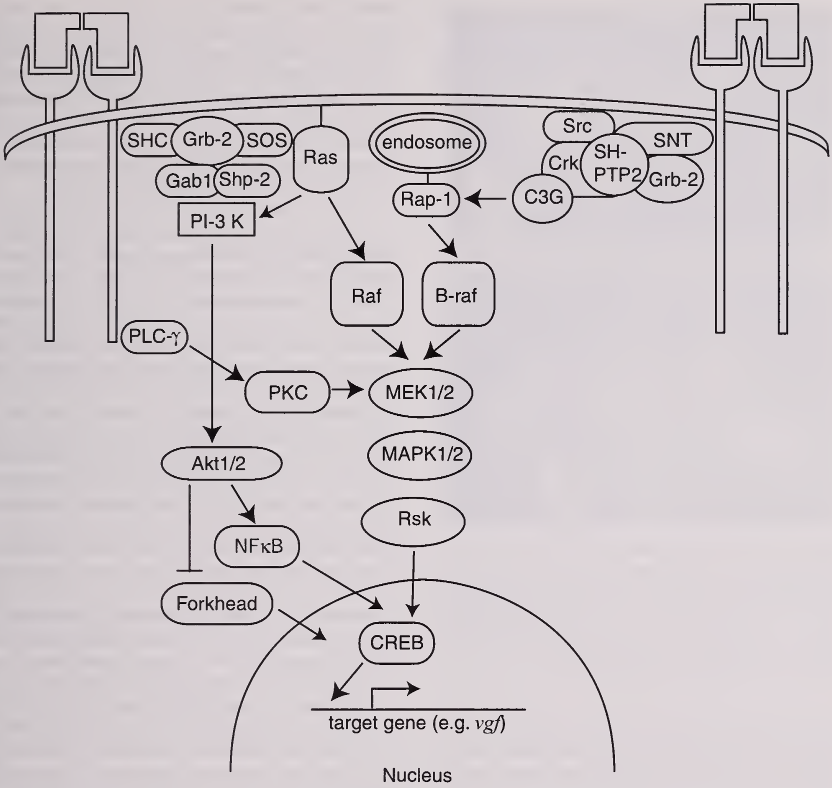

Fig. 1. Signaling cascades that are activated by neurotrophins. Neurotrophic growth factors bind as dimers to their cognate tyrosine kinase receptors, stimulating receptor autophosphorylation and generating specific phosphotyrosine sites that subsequently interact with adaptor protein complexes and activate intracellular signaling pathways.

Our work over the past several years has focused on characterizing the expression, regulation and function of neurotrophin-inducible polypeptides, with recent emphasis on a protein called VGF (non-acronymic) (7, 8). Studies of lean, hypermetabolic knockout mice that are deficient in VGF intriguingly suggest that this protein is a key regulator of energy balance. Neurotrophins may therefore play a modulatory role in the complex circuits that control energy balance in the brain, specifically in the hypothalamus, and throughout the remainder of the peripheral and central nervous systems. In support of this hypothesis, reduced BDNF synthesis in haplo-insufficient mice (9) and targeted deletion of the neurotrophin-regulated molecule VGF (10), each lead to profound alterations in energy homeostasis. Moreover, systemic administration of BDNF has been shown to improve blood glucose control and regulate energy expenditure in obese mice (11–16), and BDNF gene expression has been shown to be induced in calorically restricted mice (17). Finally, ciliary neurotrophic factor (CNTF) has been recognized to have robust, leptin-independent effects in reducing body weight (18, 19), and administration of recombinant human BDNF to patients with diabetic polyneuropathy resulted in increased gut motility as a side effect (20). Using VGF as a prototype for neurotrophin-regulated gene products that function as intermediates, linking the nervous system

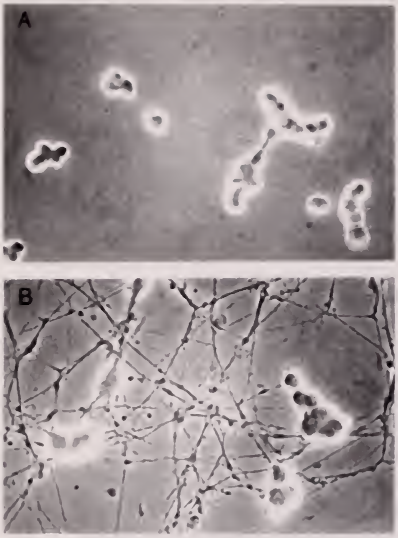

Fig. 2. The PC12 pheochromocytoma cell line. PC12 cells grown in serum-containing medium display many properties of adrenal chromaffin cells (Panel A). Treatment with NGF for two weeks leads to the cessation of cell division, intense neurite outgrowth, and the induction of gene expression and a program of neuronal differentiation that models the sympathetic neuron (Panel B).

with peripheral tissues, I would like to discuss our current understanding of the regulation, expression and function of this secreted neuronal and neuroendocrine polypeptide.

Cloning and Characterization of the Neurotrophin-Inducible Gene Product VGF

VGF was independently identified as VGF8a (7), NGF33.1 (21, 22) and a2 (23) on the basis of its rapid induction by NGF in rat PC12 pheochromocytoma cells. Among gene products that are regulated with immediate-early or delayed-early kinetics, VGF is unusual in that it is induced robustly and relatively selectively by neurotrophic growth factors (7, 22, 24), is synthesized exclusively in neuronal and neuroendocrine cells (22, 25–29), and is transported in dense core vesicles with its processed peptides released via the regulated secretory pathway (30, 31). In addition, the *vgf* coding and promoter sequences are highly homologous from mouse to human. VGF mRNA has been detected in the rat by *in situ* hybridization as early as embryonic day 11.5 (E11.5) in what appear to be migrating neural crest cells fated to become enteric ganglia (28). The earliest expression of VGF therefore appears to occur in the peripheral nervous system (PNS) as maturing neurons cluster to form ganglia. In later stages of embryogenesis, VGF mRNA is also expressed in regions of the brain, pituitary, adrenal medulla and myenteric plexus.

After birth, VGF is widely expressed throughout the rodent brain (25, 27–29, 32–34), and immunocytochemical studies indicate that the highest concentration of VGF is found in the medial hypothalamus (25, 27). Following colchicine blockade of axonal transport, VGF-immunoreactive cells can be identified as strongly stained in neurosecretory regions of the hypothalamus, including the arcuate, paraventricular and supraoptic nuclei, and in the suprachiasmatic nucleus (25, 27). In addition to abundant expression in the brain, VGF mRNA has been detected in the adult rat spinal cord, and in the peripheral nervous system, where VGF polypeptide and mRNA are found in dorsal root and sympathetic ganglia (26, 28). VGF is also expressed by endocrine cells in the pituitary, adrenal medulla and gastrointestinal tract, and in pancreatic β cells (35), indicating that peripherally synthesized VGF may function by reaching target tissues via the systemic circulation.

Since VGF expression is induced by neurotrophins *in vitro*, in PC12 cells (7, 22, 23) and in cortical neurons (24), VGF and neurotrophin receptor distributions have been compared to offer insight into potential mechanisms of VGF regulation *in vivo*. Localization of VGF, trkA, trkB and trkC mRNAs by *in situ* hybridization during rat development indicates overlap in trk and VGF mRNA expression. Although no trk mRNA is exclusively co-localized with VGF mRNA, the expression patterns in the brain, spinal cord and peripheral nervous system of mRNAs encoding the trkB catalytic isoform and VGF were found to be the most similar (36). In agreement with these studies, a recent investigation demonstrated that robust ectopic expression of VGF in embryonic cortex can be triggered *in vivo* by locally injected BDNF (37). In addition, since growth factors have been implicated not only in neuronal development but also in the response of the nervous system to injury and regulation of synaptic plasticity, regulation of VGF expression has been examined in the brain during critical developmental periods, and following seizure or lesioning. Of considerable interest, VGF mRNA levels are regulated by electrical activity in the developing visual system, by seizure and long-term potentiation (LTP) in the hippocampus, and following injury in the cerebral cortex and striatum, paradigms that lead to neurotrophin induction, synaptic remodeling and axonal sprouting.

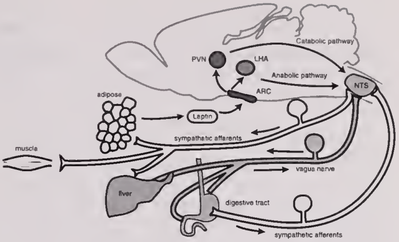

Fig. 3. Schematic diagram of the circuits that control energy balance. Leptin is synthesized by adipose tissue and binds receptors in the hypothalamus, relaying the state of peripheral fat stores to the brain. Feeding and metabolic rate are sensed and controlled in large part by the autonomic nervous system, which is interconnected with the hypothalamus and brain stem (including the NTS), and relays afferent and efferent signals to fat, muscle, liver, and the digestive tract. Catabolic pathways decrease feeding and stimulate peripheral metabolism, a response to the satiety signals from arcuate-derived neuropeptides α-MSH and CART. Anabolic signals increase feeding and decrease peripheral metabolism, leading to energy storage, primarily in response to arcuate neuropeptides such as NPY and AGRP.

Targeted Ablation of VGF Affects Energy Balance

Based on the regulatory studies described above, the phenotype of the VGF-mutant mouse, in which the entire VGF protein coding sequence was deleted by homologous recombination, was somewhat unanticipated (10). At birth, homozygous VGF-deficient mice are indistinguishable from wild-type or heterozygous littermates. Thus, the former appear to have no major defects in the patterning or wiring of their nervous system. However, VGF-mutant mice fail to gain weight efficiently, and as adults they are lean (with 50–70% of the body weight of wild-type mice), hypermetabolic, hyperactive, and infertile (10). How is body weight regulated, and what role might VGF play in the control over appetite and metabolic activity?

Several regions within the brain have classically been associated with the control of food intake and energy output, including the caudal brain stem and most notably the hypothalamus, where lesions lead to profound alterations in feeding behavior, body weight and fat storage. The state of peripheral fat stores is relayed to the brain via circulating hormones such as leptin, an adipocyte-synthesized protein which transduces its signal through transport and binding to the leptin-receptor system in the hypothalamus (38, 39) (Fig. 3). Characterization of leptin-responsive hypothalamic neurons suggests that subsets of these cells contain orexigenic neuropeptides such as neuropeptide Y (NPY) and agouti-related polypeptide (AGRP), which stimulate feeding, and anorexigenic neuropeptides such as alpha-melanocyte stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART), which decrease feeding. Balancing the output of these orexigenic and anorexigenic circuits allows food consumption to be controlled. The satiety-inducing melanocortin pathways in the hypothalamus decrease food intake through the interplay of two peptides that compete for binding to the melanocortin 4 receptor (MC4-R), α-MSH and its antagonist AGRP. Effects of these leptin-responsive circuits on energy balance are mediated by projections to other areas of the hypothalamus, and to the brainstem, spinal cord and cortex (38).

Based on the functional studies described above, one might anticipate that VGF would be synthesized in abundance in the brainstem and hypothalamus, and that expression of the *vgf* gene would be regulated in these regions in response to feeding and/or fasting. Several studies have demonstrated high levels of VGF mRNA and polypeptide expression in the hypothalamus (25, 27–29, 33, 34) and an increase in VGF mRNA levels in the hypothalamic arcuate nucleus (ARC) in response to fasting (10). VGF expression is also regulated in neurons of both the dorsal motor nucleus of the vagus (DMV) and nucleus tractus solitarius (NTS) (40, 41), which provide vagal afferent and efferent fibers that mediate gastric visceral sensitivity and secretory, trophic and motor regulation of the stomach. VGF is therefore appropriately situated to exert a functional influence on the neural pathways that regulate feeding and metabolism.

How might VGF control energy homeostasis? Relative resistance to environmentally induced or genetically induced obesity is a useful indicator of a functional role in the control of energy balance. VGF-mutant mice fail to develop diet-induced obesity that normally results from consumption of high-fat, high-carbohydrate food. In addition, VGF deficiency blocks the development of obesity which results from toxic injury to the hypothalamus. VGF ablation therefore protects mice against two independent environmental causes of obesity.

Does VGF deficiency also block the genetically induced obesity that is found in several well-studied strains of mice, including *ob/ob* mice (a strain which is profoundly obese due to a failure to synthesize the adipose hormone leptin), and A^y/a (a strain which develops maturity onset obesity due to ectopic expression of the melanocortin receptor-antagonist Agouti)? Mice with mutations in the leptin (*ob/ob*) or leptin-receptor (*db/db*) genes develop early onset obesity that is associated with reduced metabolic rate, increased food intake, diabetes, and decreased fertility (42), while mice with defective signaling in the melanocortin pathway develop a later onset obesity syndrome that is associated with hyperphagia, hyperinsulinemia and hyperglycemia (43, 44). Interbreeding of these obese mice with other strains that harbor additional genetic mutations, and analysis of the phenotypes of the resulting offspring, has been an extremely useful technique to better define the molecular components of the leptin and melanocortin pathways. Interestingly, interbreeding of A^y/a with VGF-mutant mice completely blocks the development of obesity, hyperglycemia, and hyperinsulinemia in double-mutant mice (Fig. 4, panels A and B). On the other hand, targeted ablation of the *Vgf* gene in *ob/ob* mice does reduce their weight, plasma glucose and food intake in comparison to control *ob/ob* mice, but does not decrease percentage of body fat or increase core body temperature (as a marker of metabolic activity) (Fig. 4, panels C and D). Genetic analysis therefore very strongly suggests that VGF does function in the melanocortin pathway, either in the hypothalamus itself or perhaps in autonomic outflow pathways that ultimately innervate peripheral metabolic tissues (Fig. 5).

Indirect experimental evidence suggests that VGF may somehow regulate peripheral sympathetic tone. VGF mRNA is detected at the earliest stages of development in sensory and sympathetic neurons of the embryonic peripheral nervous system. Administration of monosodium glutamate (MSG) to neonatal mice generally causes maturity-onset obesity, through toxic damage to the hypothalamus and sympathetic nervous system, and gold thioglucose (GTG) treatment injures glucose-sensitive hypothalamic neurons in adult mice, similarly leading to obesity. VGF-mutant mice become obese and hyperglycemic following MSG treatment, but not following GTG treatment, an indication that intact sympathetic outflow tracts are likely to be essential for the lean phenotype, and implying that VGF might be involved in the control of sympathetic activity.

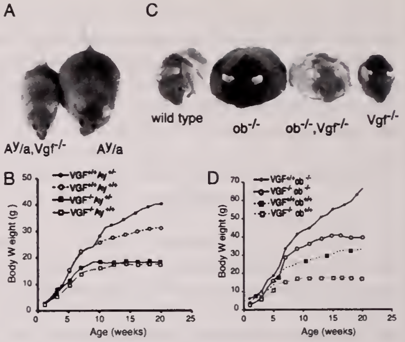

Fig. 4. Interbreeding of lean VGF-mutant mice with obese A^y/a Agouti or *ob/ob* mice indicates that targeted deletion of *Vgf* selectively blocks obesity and weight gain in Agouti mice, but has less effect on leptin-deficient *ob/ob* mice. A^y/a and double-mutant A^y/a, *Vgf-/Vgf-* mice are shown in panel A and weights of representative mice from these crosses are indicated in panel B. Wild type, *Vgf-/Vgf-*, *ob/ob*, and double-mutant *ob/ob*, *Vgf-/Vgf-* mice are shown in panel C and representative weights of mice with these genotypes are indicated in panel D.

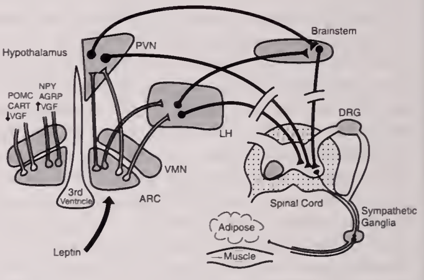

Fig. 5. Schematic diagram of hypothesized sites of VGF action in the nervous system. VGF mRNA and polypeptide levels are regulated by fasting, in the arcuate nucleus (ARC) of the hypothalamus. Based on lesion and genetic studies, pathways in black that project from the paraventricular nucleus (PVN) and lateral hypothalamus (LH) directly to the spinal cord, or to the brain stem, and ultimately relay signals to the periphery via the sympathetic nervous system, have been implicated as critical sites of VGF action in the regulation of energy output.

Mechanism(s) of Action and Future Directions

Analyses of VGF-mutant mice suggest that this protein might be a target for anti-obesity pharmaceutical intervention. How might VGF function? In rodents and humans, the highly conserved VGF polypeptide contains at least 10 potential sites for proteolytic cleavage, suggesting that one or more bioactive peptides might result from enzymatic processing prior to secretion. In fact, the C-terminal-30-amino-acid VGF-derived peptide has been isolated from bovine posterior pituitary, and several studies have identified differential tissue- and cell-specific VGF processing. Recent studies have identified VGF peptides in cerebrospinal fluid (45) and brain (46), and work underway suggests that VGF-C-terminal-derived peptides have biological activity in the gut, uterus and brain. Characterization of putative cell surface VGF receptors is obviously dependent on the initial identification of one or more bioactive fragments of VGF, and the additional detection of these peptides *in vivo*. Studies that better define the function of predicted and identified VGF peptides are currently being pursued, utilizing intra-cerebroventricular (icv) injection approaches, peripheral tissue models and transgenic mice. Alternatively, since VGF is secreted from neuronal and endocrine cells, this protein may play an indirect role, perhaps by regulating cleavage, stability, and/or secretion of other peptide hormones or neuropeptides. In fact, targeted deletion of the enzyme carboxypeptidase E results in obesity and diabetes, an indirect result of aberrant peptide processing, while another polypeptide, 7B2, has been shown to function as a specific regulator of PC-2 convertase activity in secretory granules (of note, PC-1 mutations cause obesity in humans).

Summary

Ongoing studies suggest that neurotrophins and neurotrophin-regulated gene products play a global role not just during development, but also in the adult nervous system. Understanding how these proteins contribute to processes that are controlled in part by the nervous system, such as energy homeostasis, may provide insight into and suggest new treatment modalities for obesity and anorexia.

Acknowledgments

Supported by NIH grants AG10676 and DK 57702, and NSF grant IBN-9986657.

References

1. Levi-Montalcini R. The nerve growth factor 35 years later. Science 1987; 237:1154–1162.
2. Cowan WM. Viktor Hamburger and Rita Levi-Montalcini: the path to the discovery of nerve growth factor. Annu Rev Neurosci 2001; 24:551–600.
3. Leibrock J, Lottspeich F, Hohn A, et al. Molecular cloning and expression of brain-derived neurotrophic factor. Nature 1989; 341:149–152.
4. Greene LA, Tischler AS. Establishment of a noradrenergic clonal line of rat adrenal pheochromocytoma cells which respond to nerve growth factor. Proc Natl Acad Sci U S A 1976; 73:2424–2428.
5. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 2001; 24:677–736.
6. Patapoutian A, Reichardt LF. Trk receptors: mediators of neurotrophin action. Curr Opin Neurobiol 2001; 11:272–280.
7. Levi A, Eldridge JD, Paterson BM. Molecular cloning of a gene sequence regulated by nerve growth factor. Science 1985; 229:393–395.
8. Salton SR, Ferri GL, Hahm S, et al. VGF: a novel role for this neuronal and neuroendocrine polypeptide in the regulation of energy balance. Front Neuroendocrinol 2000; 21:199–219.
9. Kernie SG, Liebl DJ, Parada LF. BDNF regulates eating behavior and locomotor activity in mice. EMBO J 2000; 19:1290–1300.
10. Hahm S, Mizuno TM, Wu TJ, et al. Targeted deletion of the Vgf gene indicates that the encoded secretory peptide precursor plays a novel role in the regulation of energy balance. Neuron 1999; 23:537–548.
11. Ono M, Ichihara J, Nonomura T, et al. Brain-derived neurotrophic factor reduces blood glucose level in obese diabetic mice but not in normal mice. Biochem Biophys Res Commun 1997; 238:633–637.
12. Tonra JR, Ono M, Liu X, et al. Brain-derived neurotrophic factor improves blood glucose control and alleviates fasting hyperglycemia in C57BLKS-Lepr(db)/lepr(db) mice. Diabetes 1999; 48:588–594.
13. Nakagawa T, Tsuchida A, Itakura Y, et al. Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. Diabetes 2000; 49:436–444.
14. Ono M, Itakura Y, Nonomura T, et al. Intermittent administration of brain-derived neurotrophic factor ameliorates glucose metabolism in obese diabetic mice. Metabolism 2000; 49:129–133.
15. Tsuchida A, Nakagawa T, Itakura Y, et al. The effects of brain-derived neurotrophic factor on insulin signal transduction in the liver of diabetic mice. Diabetologia 2001; 44:555–566.
16. Tsuchida A, Nonomura T, Ono-Kishino M, et al. Acute effects of brain-derived neurotrophic factor on energy expenditure in obese diabetic mice. Int J Obes Relat Metab Disord 2001; 25:1286–1293.
17. Duan W, Guo Z, Mattson MP. Brain-derived neurotrophic factor mediates an excitoprotective effect of dietary restriction in mice. J Neurochem 2001; 76:619–626.

18. Ziotopoulou M, Erani DM, Hileman SM, et al. Unlike leptin, ciliary neurotrophic factor does not reverse the starvation-induced changes of serum corticosterone and hypothalamic neuropeptide levels but induces expression of hypothalamic inhibitors of leptin signaling. Diabetes 2000; 49:1890–1896.
19. Lambert PD, Anderson KD, Sleeman MW, et al. Ciliary neurotrophic factor activates leptin-like pathways and reduces body fat, without cachexia or rebound weight gain, even in leptin-resistant obesity. Proc Natl Acad Sci U S A 2001; 98:4652–4657.
20. Wellmer A, Misra VP, Sharief MK, et al. A double-blind placebo-controlled clinical trial of recombinant human brain-derived neurotrophic factor (rhBDNF) in diabetic polyneuropathy. J Peripher Nerv Syst 2001; 6:204–210.
21. Salton SR. Nucleotide sequence and regulatory studies of VGF, a nervous system-specific mRNA that is rapidly and relatively selectively induced by nerve growth factor. J Neurochem 1991; 57:991–996.
22. Salton SR, Fischberg DJ, Dong KW. Structure of the gene encoding VGF, a nervous system-specific mRNA that is rapidly and selectively induced by nerve growth factor in PC12 cells. Mol Cell Biol 1991; 11:2335–2349.
23. Cho KO, Skarnes WC, Minsk B, et al. Nerve growth factor regulates gene expression by several distinct mechanisms. Mol Cell Biol 1989; 9:135–143.
24. Bonni A, Ginty DD, Dudek H, Greenberg ME. Serine 133-phosphorylated CREB induces transcription via a cooperative mechanism that may confer specificity to neurotrophin signals. Mol Cell Neurosci 1995; 6:168–183.
25. van den Pol AN, Decavel C, Levi A, Paterson B. Hypothalamic expression of a novel gene product, VGF: immunocytochemical analysis. J Neurosci 1989; 9:4122–4137.
26. Ferri GL, Levi A, Possenti R. A novel neuroendocrine gene product: selective VGF8a gene expression and immunolocalisation of the VGF protein in endocrine and neuronal populations. Brain Res Mol Brain Res 1992; 13:139–143.
27. van den Pol AN, Bina K, Decavel C, Ghosh P. VGF expression in the brain. J Comp Neurol 1994; 347:455–469.
28. Snyder SE, Pintar JE, Salton SR. Developmental expression of VGF mRNA in the prenatal and postnatal rat. J Comp Neurol 1998; 394:64–90.
29. Snyder SE, Salton SR. Expression of VGF mRNA in the adult rat central nervous system. J Comp Neurol 1998; 394:91–105.
30. Possenti R, Eldridge JD, Paterson BM, et al. A protein induced by NGF in PC12 cells is stored in secretory vesicles and released through the regulated pathway. EMBO J 1989; 8:2217–2223.
31. Benson DL, Salton SR. Expression and polarization of VGF in developing hippocampal neurons. Brain Res Dev Brain Res 1996; 96:219–228.
32. Okamura H, Tanaka M, Kanemasa K, et al. In situ hybridization histochemistry of vgf mRNA in the rat suprachiasmatic nucleus: co-localization with vasopressin/neurophysin and VIP/PHI. Neurosci Lett 1995; 189:181–184a.
33. Lombardo A, Rabacchi SA, Cremisi F, et al. A developmentally regulated nerve growth factor-induced gene, VGF, is expressed in geniculocortical afferents during synaptogenesis. Neuroscience 1995; 65:997–1008.
34. Snyder SE, Cheng HW, Murray KD, et al. The messenger RNA encoding VGF, a neuronal peptide precursor, is rapidly regulated in the rat central nervous system by neuronal activity, seizure and lesion. Neuroscience 1998; 82:7–19.
35. Possenti R, Rinaldi AM, Ferri GL, et al. Expression, processing, and secretion of the neuroendocrine VGF peptides by INS-1 cells. Endocrinology 1999; 140:3727–3735.
36. Snyder SE, Li J, Salton SR. Comparison of VGF and trk mRNA distributions in the developing and adult rat nervous systems. Brain Res Mol Brain Res 1997; 49:307–311.
37. Eagleson KL, Fairfull LD, Salton SR, Levitt P. Regional differences in neurotrophin availability regulate selective expression of VGF in the developing limbic cortex. J Neurosci 2001; 21:9315–9324.
38. Ahima RS, Saper CB, Flier JS, Elmquist JK. Leptin regulation of neuroendocrine systems. Front Neuroendocrinol 2000; 21:263–307.
39. Schwartz MW, Woods SC, Porte D, Jr., et al. Central nervous system control of food intake. Nature 2000; 404:661–671.
40. Kanemasa K, Okamura H, Kodama T, Ibata Y. Induction of VGF mRNA in neurons of the rat nucleus tractus solitarius and the dorsal motor nucleus of vagus in duodenal ulceration by cysteamine. Brain Res Mol Brain Res 1995; 32:55–62.
41. Kanemasa K, Okamura H, Kodama T, et al. Time course of the induction of VGF mRNA in the dorsal vagal complex in rats with cysteamine-induced peptic ulcers. Brain Res Mol Brain Res 1995; 34:309–314.
42. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998; 395:763–770.
43. Barsh G. From Agouti to Pomc — 100 years of fat blonde mice. Nat Med 1999; 5:984–985.
44. Salton SR, Hahm S, Mizuno TM. Of mice and MEN: what transgenic models tell us about hypothalamic control of energy balance. Neuron 2000; 25:265–268.
45. Stark M, Danielsson O, Griffiths WJ, et al. Peptide repertoire of human cerebrospinal fluid: novel proteolytic fragments of neuroendocrine proteins. J Chromatogr B Biomed Sci Appl 2001; 754:357–367.
46. Trani E, Giorgi A, Canu N, et al. Isolation and characterization of VGF peptides in rat brain. Role of PC1/3 and PC2 in the maturation of VGF precursor. J. Neurochem 2002; in press.

Grand Rounds

Behavioral Cardiology — Has Its Time Finally Arrived?

Thomas Pickering, M.D., D.Phil., Lynn Clemow, Ph.D., Karina Davidson, Ph.D., and William Gerin, Ph.D.

Abstract

Traditional cardiology has taken a mechanistic approach to heart disease. But the new discipline of behavioral cardiology takes a broader view, concluding that heart disease is not inevitable, but develops largely from unhealthy lifestyles, such as smoking, overeating and physical inactivity, and from psychosocial stress. Physical inactivity and excessive caloric intake are also responsible for the epidemic of obesity, which is associated with a dramatic increase in the prevalence of diabetes. This increase in the incidence of diabetes may, in turn, reverse the recent decline of cardiovascular deaths in the US. A variety of psychosocial stressors have been implicated in the development of cardiovascular disease. These include occupational stress, anxiety, social isolation, hostility, anger, and type A behavior. There is clearly some overlap between these stressors, all of which may affect the heart adversely. Both the lifestyle and psychosocial factors can be altered by behavioral treatment, in which the patient and the practitioner work together. Unfortunately, various barriers can impair the successful implementation of behavioral treatment. These barriers include poor compliance by the patient, lack of skill in providing effective interventions by the health care provider, and lack of incentives within the health care system, particularly reimbursement.

Key Words: Behavioral cardiology, smoking, diet, exercise, stress, depression, anger, rumination, coronary heart disease.

Coronary heart disease (CHD) continues to be the major cause of death in this country, and stroke one of the leading causes of disability. Recently, we have seen dramatic technological and genetic advances in the diagnosis and treatment of cardiovascular disease, as exemplified by the increasing use of stents and statins and research breakthroughs in gene therapy. These efforts have focused on the heart and blood vessels, with increasing emphasis on molecular processes that lead to the formation of atherosclerotic plaque and its subsequent rupture. Such effort, which implies that the development of heart disease is inevitable but modifiable with high technology, is fueled by widely quoted figures showing that death rates from heart disease have decreased steadily over the past 30 years (1). However, it does not address many of the root causes of heart disease. Furthermore, there is no evidence that the incidence of new cardiovascular events has decreased; indeed, for African-Americans it may actually be increasing (1). Thus, the reduction of morbidity is due exclusively to improvements in treatment after the disease is clinically manifest. While these advances are impressive, they are very costly. Health care costs are continuing to increase at a rate faster than that of inflation. One of the most rapidly increasing components is the cost of prescription drugs, many of which are used for treating cardiovascular disease (2). In addition, as the prevalence of childhood obesity continues to grow, the incidence of new cases of heart disease will probably start increasing in the near future: childhood obesity is a predictor of coronary artery disease in young adults (3). There is therefore an urgent need to pursue other ways of preventing and treating heart disease. In this paper we review the role of behavioral and lifestyle approaches to these goals.

What is Behavioral Cardiology?

Behavioral cardiology represents an alternative, and often overlooked, medical view that

---

From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address correspondence to Thomas G. Pickering, M.D., D.Phil., Zena and Michael A. Wiener Cardiovascular Institute, Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Adapted from a Grand Rounds presentation to the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, NY on February 12, 2001, and updated as of April 26, 2002.

coronary heart disease is not inevitable, but can be prevented. According to this view, the causes of heart disease lie not so much in the heart itself, but in the brain, or more specifically, the mind. There are two general ways that the mind affects the heart. The first is via our lifestyles, and the second is via the effects of psychosocial stresses and how we cope with them.

The concept of behavioral cardiology links these two processes, not only in how they interact to cause heart disease, but also in terms of how they can be altered to modify heart disease once it is present (Fig. 1). Behavioral cardiology is an outgrowth of behavioral medicine, which was first defined at a conference held at Yale in 1977 (4): "Behavioral medicine is the field concerned with the development of behavioral-science knowledge and techniques relevant to the understanding of physical health and illness and the application of this knowledge and these techniques to prevention, diagnosis, treatment and rehabilitation." Behavioral cardiology differs from the better-known discipline of preventive cardiology in that it takes a wider and more integrative approach. Preventive cardiology focuses on traditional lifestyle risk factors such as smoking and cholesterol, and pays little attention to psychological risk factors (such as anger) or techniques for treating the disease (such as stress management). Another related area, psychosomatic medicine, covers the role of psychological factors in the development of physical disease, but pays little attention to lifestyles or treatment. Thus, behavioral cardiology includes the areas covered by both preventive cardiology and psychosomatic medicine.

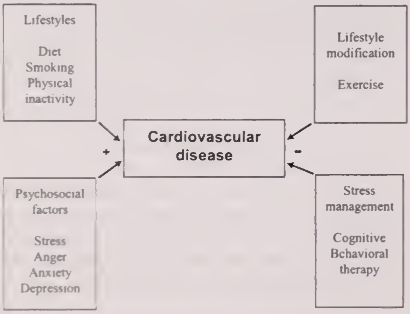

Fig. 1. Ways by which lifestyles and psychosocial factors (left-hand panels) can affect the development of cardiovascular disease, and how they can be modified (right-hand panels) to treat it.

Because behavioral cardiology covers such a wide range of disciplines, and also because medicine is becoming increasingly sub-specialized, no one person has the expertise to master the entire field of behavioral cardiology. Its approach, therefore, differs from that of most other areas of medicine in that it is essentially interdisciplinary, and typically involves an active collaboration between physicians, psychologists, nurses, and dietitians, with the cardiologist as the "gatekeeper."

Lifestyle and Heart Disease

The three biggest risk factors for atherosclerotic cardiovascular disease — cholesterol levels, smoking, and blood pressure — are all influenced by the way we choose to live. Smoking is of course purely behavioral in origin, although physiologic processes come into play to establish an addiction. And both cholesterol level and blood pressure are influenced by what we eat and how much we exercise. In an assessment of the causes of death in the US in 1993, McGinnis and Foege (5) estimated that approximately 50% of all deaths (the majority of which are due to heart disease) were attributable to behavioral or lifestyle factors, including tobacco and alcohol use, poor diet, and physical inactivity. Another example of the impact of lifestyles on the development of coronary heart disease is provided by the Nurses' Health Study, which is a prospective study of nurses in the US (6). In a 14-year follow-up of 85,000 nurses, it was found that women who adopted one or more characteristics of a "healthy" lifestyle (i.e., not smoking, not drinking, exercising regularly, not being overweight, and/or following a good diet), had an 83% lower risk of developing heart disease than women who did not do any of these. Unfortunately, only 3% of the nurses actually adopted all of these healthy lifestyles. The major lifestyle factors are summarized below.

Smoking

Smoking kills more than 400,000 Americans every year, and more than half of these deaths are due to cardiovascular disease and stroke. The economic cost of tobacco smoking has been estimated to be more than $50 billion annually. Smoking is responsible for about 30% of cardiovascular morbidity and mortality (7). It more than doubles the incidence of coronary artery disease, and increases mortality by 70%

(8). It also reduces the effectiveness of costly interventions such as coronary angioplasty, after which, when compared with nonsmokers, smokers have twice the risk of death or a recurrent myocardial infarction (MI) (9). The risks associated with smoking are almost completely reversible after a person quits (10); smoking cessation has been shown to be one of the most cost-effective interventions in the whole field of medicine (11). Despite this, health insurance rarely reimburses people who enter programs to quit smoking.

Dietary Factors

Dietary factors have a substantial impact on the development of CHD. The total cholesterol level in the blood is the most extensively studied risk factor, and while genetics plays at least a partial role, there is considerable evidence that the intake of saturated fat is also an influence. In a study done in 40 countries, it was found that there is a close and linear correlation between saturated fat intake, blood cholesterol, and the death rates from coronary heart disease in each country (12). On the other hand, several other dietary factors have been correlated with low CHD incidence. These include fiber, nuts (13), fish (14), and grain (15). The Mediterranean diet, which is low in saturated fat and cholesterol, and high in fruits, vegetables, and grains, has been shown in both observational and experimental studies to be associated with a low incidence of CHD (16).

Obesity

In 1998 the American Heart Association first defined obesity (17) as "a major modifiable risk factor for coronary heart disease ... on a par with cigarette smoking, physical inactivity, and high blood cholesterol." One of the reasons why obesity is so important is that it is associated with a cluster of risk factors, including dyslipidemia, diabetes, and hypertension, which when they come together make a lethal combination, particularly in women. While studies of twins have documented the importance of genetic factors (18), the major causes of obesity are excessive caloric intake and inadequate physical activity, both of which are features of the contemporary American lifestyle (19). The prevalence of obesity has increased markedly in the US and other countries over the past 20 years: in 1978 one-fourth of Americans were overweight (as defined by a body mass index [BMI] between 25 and 30 kg/m^2), while in 1990 one-third were overweight (19). The latest figures from the Centers for Disease Control and Prevention (CDC) show that 60% of all Americans are now overweight (20). Similarly, the prevalence of obesity (defined as a BMI > 30 kg/m^2) has increased from 12% in 1991 to 19% in 1999 (20). It has been estimated that 300,000 deaths per year are attributable to obesity, accounting for nearly 10% of national health costs (20). The epidemic has its roots in childhood, and can be attributed both to physical inactivity, such as the number of hours per day spent watching television (21), and to caloric intake, such as the amount of sweetened soda drinks consumed (22).

Exercise

Physical inactivity is widely recognized as a major risk factor for cardiovascular disease, and numerous studies have shown that even mild exercise can reduce the probability of morbid events, and even increase longevity. In the results from the Honolulu Heart Study, the risk of coronary heart disease was twice as high for men who walked less than a quarter of a mile per day than for those who walked at least 1.5 miles (23). Only 22% of adults engage in 30 minutes or more of light-to-moderate exercise five or more times per week (the amount recommended for cardiovascular benefit) (24).

Psychosocial Risk Factors and Coping Strategies

The mind also influences heart disease, through the effects of stress and the way in which the body copes with it. An individual experiences psychological stress, which is perceived as the signal of a threat to well-being; stress is thus the end result of an interaction between the source of the stress and the individual. In general, an individual feels incapable of fully controlling an undesirable event before it is perceived as stressful. The effects of stress on the body depend not only on how a person perceives stress, but on the person's response in coping with it.

CHD is much more common in people who are least well off. This is an almost universal finding that relates not only to cardiovascular disease, but also to other chronic diseases. This has been shown in populations as diverse as civil servants in the UK (25) and urban communities in the US (26). These gradients persist even after controlling for traditional lifestyle-dependent risk factors such as smoking, cholesterol, and blood pressure. More impressive, they are still present after adjusting for traditional markers of socioeconomic status, such as education and income. Social isolation may be a contributory factor (27).

A variety of manifestations of chronic stress have been proposed as possible cardiovascular disease risk factors; these include depression, anger/hostility, type A behavior pattern, and anxiety. While each of these factors is theoretically distinct from the others, they frequently overlap in the same individual. This has to be taken into account when reviewing the evidence supporting their roles in the development of heart disease (28).

Stress

In a Canadian public survey, stress was mentioned as a major factor causing heart disease more frequently than high blood pressure and high lipids (29). However, the scientific investigation of stress as a cardiovascular risk factor has been limited by problems of definition. Stress is essentially a subjective phenomenon, and while some environmental occurrences are universally regarded as being stressful (such as earthquakes), others (such as public speaking) may be very stressful for some people, but not for others. For the layperson, stress may be associated with work and family, social isolation, and the occurrence of recent, acute and chronic life events.

Work stress, which may be defined as a perception of low control over one's work environment coupled with high work demands, has been a reliable and consistent predictor of hypertension (30) and carotid atherosclerosis (31), as well as cardiac events and death (32). Of the two components of work stress, demands and control, the latter appears to be more important, since low job control, by itself, has also been found to predict future cardiac events (33). Family stress has been less well studied, but has been found, for women, to be relatively more important than work stress for predicting recurrent coronary events (34).

Social isolation (having few friends, family, or significant others) and perceived lack of social support have consistently been found to predict acute myocardial infarction and cardiac death. As noted by Rozanski et al. (35), the relative risks in 15 recent studies indicate a threefold increase in mortality risk for patients with cardiovascular disease who are socially isolated and/or perceive poor social support.

Acute mental stress (such as from the sudden loss of a loved one or after an earthquake) has consistently been shown in epidemiological studies to provoke silent myocardial ischemia and to predict increased cardiovascular disease incidence and death (36).

Depression

Depressive symptoms and depressive disorders predict cardiac recurrence and mortality, in cardiac patients, with relative risk ranging from 2.6–7.8 (37, 38). These risk ratios remain even after controlling for all other known predictors of myocardial infarction recurrence, and depressive symptoms predict MI recurrence in a dose-response fashion. Thus, there is considerable evidence that a cardiac patient who is depressed is at substantially higher risk for a future cardiac event. The causes for this are not clearly understood, but may include disrupted diurnal rhythms of hormonal and metabolic processes, autonomic imbalance, and poor compliance with prescribed medications (39, 40). It is not known whether treating depression will reduce this risk.

Anxiety

There have been relatively few investigations of the relationship between anxiety and cardiac disease and recurrence (38, 41, 42). Most studies of anxiety disorders have examined the increased mortality from cardiovascular disease in psychiatric patients known to have some type of anxiety disorder (43, 44), although some recent studies have found a positive relationship between anxiety and sudden cardiac death in cardiovascular disease patients (38, 41, 42). However, anxiety symptoms were not associated with MI recurrence in these studies. Rozanski and others (35, 45) hypothesize that anxiety disorders and the associated symptoms may cause an alteration in cardiac autonomic tone through impaired vagal control or reduced heart rate variability, or both, thereby causing increased risk of sudden cardiac death for cardiac patients.

Type A Behavior Pattern

Friedman and Rosenman (46) first proposed, in 1959, that a constellation of competitive, hostile, time-pressured behaviors comprise a personality trait ("Type A") that predisposes patients to cardiovascular disease. Although early studies found this to be the case, several more recent studies did not (47). Many theorists have suggested that hostility, or the tendency to view others with suspicion and skepticism, may be the toxic component of the Type A behavioral pattern, and that this component should be evaluated independently for its predictive value for cardiac patients. Four small studies of cardiovascular disease patients have found that a high level of hostility is associated with more rapid progression of atherosclerosis, more ischemia, a faster rate of restenosis after angioplasty, and a higher probability of recurrent MI (48–51).

Anger

Anger is becoming almost a national obsession. In the past few years we have seen the introduction of terms such as "road rage," "air rage," and "going postal." Anger management programs have become a part of the rehabilitation of criminals, despite a complete lack of evidence of their efficacy. However, there is evidence that episodes of anger may trigger acute myocardial infarcts (52). Moreover, anger expression style has been implicated as an independent risk factor for hypertension and cardiovascular disease. Recent investigations have shown that "anger-out" (expressing your anger explosively and outwardly) is positively associated with adverse cardiovascular outcomes (53). "Anger-in" (suppressing angry feelings) has been found to be positively associated with heart disease for women (53) and with elevated resting blood pressure for both men and women in general (54). Thus, expressing anger outwardly (but in a destructive manner) and keeping it in and brooding over it are both potential risk factors.

Rumination

Many sources of stress, such as anger-provoking events, are short-lived. However, it is possible for adverse emotions to affect a chronic process such as cardiovascular disease. Brief episodes of anger or other negative emotions can lead to sympathetic nervous system arousal and the acute rupture of an unstable atherosclerotic plaque — but most people are exposed to such events relatively infrequently. One way by which the effects of such events may be prolonged is by rumination or brooding long after they have ended. There is evidence that this process may sustain the elevated heart rate and blood pressure that accompany the actual stressful incident (55). Worry and rumination have been associated with occurrence of a second MI (56), and have been associated with decreased heart rate variability and decreased vagal tone, which is an independent risk factor for coronary events (57).

Barriers to Implementing Behavioral Approaches to Prevention and Treatment

The roles of behavioral and psychosocial factors in the causation of heart disease are often belittled. Similarly, behavioral approaches to treatment and prevention are often ignored. It is easier, for example, to write a prescription for a statin drug than it is to counsel the patient about diet, and admittedly, the medication is often more effective. Even with drug treatment, however, there is a big gap between the care that is prescribed and what is actually achieved. A classic example is the control of hypertension: despite the availability of numerous powerful medications, blood pressure is adequately controlled in fewer than one-third of the patients (58). And the availability of medications to treat some of the cardiovascular risk factors does not remove the need for additional, non-drug forms of treatment. An example of the potency of behavioral treatment comes from the Oslo Study, in which men at high risk for coronary heart disease who were randomized to lower their fat intake and stop smoking had a nearly 50% reduction in heart attacks compared to a "usual treatment" group (59). The problem is thus not that behavioral change is ineffective, but that it is difficult to achieve and to sustain, and most physicians have little training in implementing it.

Collaborative management is a basic issue in the treatment of behavioral and lifestyle factors. Heart disease is usually chronic, and its successful management thus requires a long-term collaboration between the patient, the physician and the other health care providers. Some of the barriers to successful implementation of recommended lifestyle changes are summarized in the Table. These can be loosely categorized as relating to the patient, the provider, or the health care system, and they extend across four broadly defined domains, i.e., environmental factors, cognitive factors, emotional/motivational issues, and behavioral factors.

TABLE

Barriers to Implementation of Behavioral Changes

	Environmental	Cognitive	Emotional/Motivational	Behavioral
1. Patient	Lack of access to care Social/cultural factors fast food sedentary lifestyle smoking ethnic food preferences Lack of social support for change	Lack of knowledge Low self-efficacy (confidence in the ability to effect changes) Limited acceptance of personal risk	Lack of motivation, set prevention / health as low priority Fears of giving up habits, behavioral "crutch" Stigma of "mental health" diagnosis or treatment Failure to change successfully may lead to shame, demoralization	May be unskilled in behavior change methods May have few healthy methods of stress reduction
2. Physician	Time constraints Definition of problem Few incentives May not have providers available for referral	May lack knowledge of possible interventions May perceive methods to be ineffective Not in area of expertise, "not my organ system"	May feel overwhelmed or demoralized about own effectiveness, fatalistic May feel frustrated with patients	Limited skills in behavior change, physician-delivered counseling May have limited skills in identifying and treating anxiety, depression and stress-related illness
3. Health care system	Few office system supports Not included in quality / accreditation standards Poor/no reimbursement for behavior change, nutritionist services Mental health carve-outs may prevent coordinated care within system	Behavior change is the patient's problem Health promotion focus limited, mostly self-help	Short-term financial pressures Insurers perceive subscribers as fickle, frequently change health plans, fear they will pay for service, then not reap cost savings in long term Cost-containment strategy is to restrict access	

The Patient

Getting patients to engage in behavior change, such as improving diet, losing weight, and exercising, is hindered by several barriers. Many physicians assume that patients are aware of the need for such changes and that they are likely to act in accordance with that awareness. However, it has long been recognized that knowledge alone does not provide sufficient motivation to change behavior (60). One fundamental problem is that intervention studies commonly produce improvements that only last for a few weeks to a few months, but that by one year there is almost always some degree of relapse. An example from the Trials of Hypertension Prevention (61), in which patients were asked to reduce their weight or their salt intake, is shown in Fig. 2.

The basic issue is, how do we persuade people to change behavior patterns that are usually deeply ingrained and which, at least over the short term, confer some reward? Merely providing the patient with information and instructions has yielded disappointing results. The causes for the lack of success are complex. They include the fact that patients are trying to make and sustain behavior changes in an environment that rarely makes those changes easy. The fact that obesity is an endemic problem in the US is largely a function of the availability of cheap "convenience food" that is high in fat and calories, coupled with urban and suburban environments that discourage physical activity as an in-

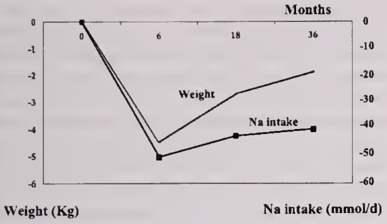

Fig. 2. Typical time course of behavioral interventions. For both weight loss and reduced sodium (Na) intake, there is a good response at 6 months, much of which is lost by 36 months. Data plotted from trials of hypertension prevention.

tegral part of everyday life. Add to this, work environments that are frequently unfriendly to physical activity and which require longer and longer work weeks. Such environmental factors create an atmosphere that offers little social support or encouragement for those individuals trying to make healthy lifestyle changes.

Another fundamental issue concerns the attitudes and motivation of the patient. Patients may have a general awareness that certain behaviors are unhealthy for some people, but may not appreciate their own personal risks. For example, patients may know that smoking is unhealthy, but may believe that the extent of their exposure is not a health problem, particularly if there are some long-lived relatives who smoke or had smoked. Others may have minimized the importance of their own risk behaviors, or placed a relatively low priority on changing these behaviors. Other patients may be demoralized because of previous failed attempts to change their behavior and may, therefore, have little confidence in their ability to make that change. There is ample evidence that people with low “self-efficacy” (self-confidence about their ability to cause change), are extremely unlikely to try to change their behavior (62). Other emotional and motivational issues of patients have to do with being afraid to give up habits that they rely on to cope with the stress in their lives. A final attitudinal and emotional barrier involves the enduring stigma associated with diagnoses of anxiety or depression, and accepting treatment for those problems. There is considerable evidence that many people are far more accepting of treatment for anxiety or depression when the treatment is integrated into their medical care (63).

A final set of patient barriers involves having limited skills in methods of effectively changing behavior. There is a large body of scientific knowledge proving the effectiveness of certain approaches to behavior change, many of them based on social learning theory (62), but these methods of self-management are generally not taught in the public education system, and the layperson’s grasp of them may be very limited (i.e., magazine articles or self-help books). For most people, these techniques work best when some coaching or professional assistance is provided. Similarly, many people lack effective stress management skills, or the methods they use to manage distress are behaviors that put their health at risk (e.g., excessive eating, alcohol intake, smoking).

The Provider

Physicians often take a negative attitude concerning the behavioral changes that they can effect through brief counseling. This attitude may be the single greatest barrier to implementing behavioral interventions. This barrier is maintained, for most physicians, by a lack of training in the use of brief counseling interventions, since such techniques have been taught at medical schools and in postgraduate programs only recently. There is abundant evidence from studies over the past 15 years that meaningful change is attainable after a brief physician-delivered intervention. Yet, without experience with such interventions, physicians are likely to feel ill-equipped to handle behavioral issues, and with such a low sense of self-efficacy they are not likely to attempt to counsel patients. In the subspecialty setting, the physician may also perceive that addressing the patient’s behavior is out of his or her area of interest and expertise (this is even more the case for depression or other emotional disorders).

Another barrier is the environment in which the doctor-patient encounter occurs. There is an increase in time-constraint pressure felt by all practicing physicians, particularly those in the primary care setting. In addition, there are few incentives for physicians to take the time to address these issues. Information systems that would support the physician and other providers in prevention activities, or help prompt physicians to inquire about and intervene with behavioral risk factors are rarely in place. There is evidence that without such office system support, even well-trained physicians make little impact on their patients’ behavior (64).

The Health Care System

The numbers and costs of invasive cardiac procedures are staggering. According to the latest figures from the American Heart Association, 539,000 coronary angioplasties were performed in 1998 in the US, a nearly 200% increase from 10 years earlier, at an average cost of $20,000 per procedure (65). Concern about the rising costs of health care is widespread, but the emphasis has almost always been on rationing the supply of health care, as opposed to reducing the demand. A seminal article by Fries et al. described a number of ways by which the need and demand for health care could be reduced (66). Several studies (67, 68) have documented that unhealthy lifestyles increase health care costs; self-management intervention programs can lower the use of medical services; and worksite-based health promotion programs can decrease the costs of both outpatient and inpatient visits.

It is ironic that our current health care system reimburses patients for expensive invasive procedures such as coronary angioplasty, but will not pay for smoking cessation programs (or in many cases, for medications such as buproprion), even though there is ample evidence, quoted above, that patients who continue to smoke have approximately twice the risk of a recurrent MI or death, and that quitting smoking is one of the most cost-effective interventions in the whole medical field. A recent survey of managed care organizations found that only 25% provided full coverage for nicotine replacement therapy and 18% for buproprion (69), despite the fact that both are recommended as standard treatments by the US Public Health Service guidelines (7),

There is a long-standing assumption in the health care profession and the insurance industry that the patient's health-related behavior is his or her own problem to solve. Reimbursement for nutritionist services has historically been extremely limited, with exceptions made for some services for patients with diabetes and hyperlipidemia. Managed care organizations, despite an initial promise to focus more on preventive services, primarily involve themselves in health promotion for the purpose of marketing to attract younger and healthier subscribers. The benefits most often take the form of some level of discount for commercial weight-loss or health-club memberships. Such services are clearly not adequate for patients who need help with addressing multiple risk factors.

The managed care industry's attitude toward preventive health services is apparently driven by their conviction that patients change insurance plans frequently and that the managed care organization that will have to pay for the preventive services (e.g., smoking cessation) will not capture the savings if the patient changes plans. Their focus is on a same-year cost savings, in line with their focus on near-term profits in a highly competitive business environment. Very few preventive or educational services meet this one-to-two-year savings criterion, and those that have been implemented have been primarily in disease management services (e.g., asthma, congestive heart failure) for patients whose poor management might lead to frequent emergency department or inpatient visits.

A second group of reimbursement barriers arises because the specialists in behavior change are often psychologists or other mental health professionals. Mental health services are usually listed separately and assigned to subcontractors for management. Despite the name "behavioral health" applied to many of these programs, the incentives in this part of the industry are designed to reduce psychiatric inpatient costs, and there is no motivation for the managed care industry to approve behavioral or psychological services aimed at saving money for or improving quality of life for medical patients. An additional, related barrier is that mental health contracts are often negotiated separately from medical system contracts. This makes it more difficult to coordinate care within a system and can limit the feasibility of collaborative multidisciplinary care.

Behavioral Approaches to Preventing and Treating Heart Disease

Specialized Behavioral Medicine Interventions

Two theoretical models have improved the science of behavior change. These are the Stages of Change models, i.e., Prochaska's Transtheoretical Model (70) and the Social Learning Theory Model of Bandura (62). The stages of change models are concerned with a person's state of readiness to change and the fact that different barriers to change predominate, depending on the patient's attitudes toward making the change. Thus, while one addicted smoker may be ready to quit, another may have no such desire or intention and may not even be contemplating change. Suggesting nicotine replacement would be a potentially effective strategy for the first patient, but is almost certain to be unsuccessful for the second, who might respond better to a conversation about her knowledge and beliefs about whether smoking is a health risk for her. The stages of change models offer two advantages over previous health belief theories: (a) First, they emphasize the fact that adopting a new health behavior is a process, not an event, and that there are milestones along the way to change. They promote the view that if we (as providers) can help a patient move from "not thinking about change" to "actively considering it," then we have accomplished something important. (b) Second, the change models also help to effectively identify likely barriers to change by asking a few brief questions. This allows the physician to focus on the issues most likely to influence patient attitudes and behavior in the long run. It is worth noting that many earlier interventions that attempted to change behavior failed because they did not consider the person's stage of change, but instead implicitly regarded all persons as being at the "action" stage. Matching the intervention to the person's stage of change has been shown to improve the likelihood that the intervention will be successful (71).

The social learning theory model has given rise to behavior change methods that include cognitive, interpersonal, and environmental influences on behavior (62). Basic components of this approach include self-monitoring (e.g., keeping food diaries) and self-analysis of behavior; self-management (including stimulus control of external cues); replacement of less desirable behavior (e.g., consumption of high-fat foods) with more desirable behaviors; and reinforcement of desirable behaviors (60). Stress reduction strategies may also be incorporated. One of the central concepts thought to influence behavior change of all kinds is "self-efficacy" (72), which refers to the person's degree of confidence in their ability to gain control over specific behaviors, such as eating and dieting. Increased self-efficacy has been found to be a critical element in motivation to engage in healthy behaviors (72). A broad range of cognitive-behavioral techniques have been combined to form the basis of most comprehensive, empirically validated treatment packages for smoking cessation, weight management, stress reduction, anger management, exercise promotion, and treatment of depression and anxiety disorders.

Physician-Delivered Interventions

Recognizing that not every patient needs or has access to a specialized behavioral treatment for risk factors, a number of investigators have "boiled down" the basic principles of behavioral counseling for health behavior problems and instructed physicians and other providers in the medical setting in these techniques.

Not surprisingly, the best established example of a behavior that "needs" to be modified is smoking. The message is simple: don't smoke. A meta-analysis of interventional studies (69) showed that when compared with no counseling, 1–3 minutes of physician advice on quitting increased the quit rate by a factor of 1.3 (from a spontaneous quit rate of 11% to 14.4%), while 4–30 minutes raised it by 1.7 (to 18.8%) (73). Although these numbers may seem small, the health consequences of a few additional people quitting smoking are so enormous that this intervention is one of the most cost-effective in clinical medicine (73). Despite this, a recent survey of office visits showed that counseling about smoking was given in only 3.8% of visits, and about diet in 20% (74). Behavioral treatment of other risk factors such as high lipids is inevitably more complex — we cannot say "don't eat" to a patient with an elevated cholesterol level. Nevertheless, the big issues here, as shown by numerous studies, are motivation and relapse prevention. Physicians' utterances generally carry weight with their patients, and since they usually meet on a regular basis, continued counseling has the potential of helping the patient maintain the behavior change.

An example of the effectiveness of brief physician counseling is provided by the WATCH (Worcester Area Trial for Counseling in Hyperlipidemia) study (64). Physicians allocated to two intervention groups attended a 3-hour training program. The intervention consisted of either physician counseling alone (average time 8 minutes per patient) or counseling in combination with an office support program (handouts and the provision of dietary assessment questionnaires for the patients while they were in the waiting room). After one year, patients in the counseling-plus-office-support-group had lost 2.3 kg more than the "usual care" (control) group ($p<0.001$), and lowered their LDL cholesterol by 3.8 mg/dL ($p=0.10$).

Thus, there is ample evidence that health care providers can and should use behavioral techniques to improve self-care as a treatment for chronic illnesses such as heart disease. These techniques include "contracting" with the patient to reach specific goals, evaluating the patient's readiness for self-care, breaking self-care tasks into small, manageable steps, and providing personalized feedback to the patient; self-monitoring of health-related behaviors; enlisting social support; and checking the patient's commitment to key tasks. One of the first tasks is to define the problems clearly. Physicians are usually concerned with such items as poor compliance and unhealthy behavior, while patients are more concerned about symptoms and emotional distress. Few physicians ask patients to identify the biggest problems they face in managing their behavior or illness.

Health Care System Interventions

Given the lack of training in behavioral techniques and the severe time limitations of cardiologists, the solution to this dilemma ideally should be a team approach. Behavioral interventions tend to require relatively large amounts of time, but a lot can be achieved by persons whose training and time is less costly than that of physicians. These may include nurses, psychologists, dietitians, and social workers, who bring the advantage of additional knowledge and skills to the patient-care process. While such team management is by no means routinely provided, there are examples of it in a variety of health care settings. The separately assigned mental health arrangements indicated previously have been discarded by some of the best of the staff-model HMOs (e.g., Group Health Cooperative of Puget Sound, Kaiser of Northern California). In their place have come integrated models of care which include one full-time equivalent behavioral/psychiatric specialist (usually a behavioral psychologist) for every 5 primary care physicians. Most routine psychological and behavioral services are integrated with medical services, while subspecialty services are reserved for the management of patients with chronic and severe psychiatric problems (75). Likewise, multidisciplinary management is being implemented in certain groups of chronically ill patients (e.g., those with asthma, CHF, hypertension, diabetes) in innovative methods of care in staff-model HMO health systems (76). The challenge is to figure out how to implement such approaches in the discounted fee-for-service reimbursement environment in which most physicians find themselves.

Information system advances (e.g., electronic medical records, computerized flow-chart systems, hand-held computer devices) may assist providers as they come online, with an ability to track risk-factor status over time, and provide ready access to counseling algorithms and patient-education materials. Initiatives such as the "Improving Chronic Illness Care" model sponsored by the Robert Wood Johnson Foundation support the dissemination of such resources in community health care systems (77). This technical support includes: information systems for tracking patient data and decision support for clinicians; health care delivery design; and resources to support self-management and behavior change among patients.

On a policy level, much remains to be done. The general lack of reimbursement for behavioral forms of treatment, including smoking cessation, implies a double standard on the part of the insurance companies. Any intervention, be it therapeutic or preventive, should be safe and effective. Third-party payers have never suggested that a coronary bypass operation should be reimbursed on the grounds that it will save the company money in the future. And yet the argument that they use for not reimbursing a smoking cessation program is precisely that — it will cost the company money. Changing this paradoxical situation will require action on many fronts: at the grass roots level by patients; by health care professionals; and ultimately, by legislative action.

Conclusions

The field of cardiology has made great strides in the past decade. The advances that have received the most attention are high-tech innovations in diagnosing and treating heart disease, such as ultrafast computed tomography (CT) scans and coronary artery stents. There is no question that these procedures have saved lives and reduced morbidity for a substantial number of people. At the same time, we have no evidence that the incidence of CHD is decreasing. In fact, it may well increase in the future. It seems clear that technology by itself will not solve the problem of CHD. Gains have also been made on the equally important but less glamorous front of behavior change. While inserting a stent in the patient's coronary artery undoubtedly represents a remarkable and valuable achievement, reducing the need for such a procedure altogether by getting people to improve their diets, quit smoking, exercise, and manage their stress would represent no less a milestone.

Utilizing a team approach, cardiologists can make recommendations and referrals for such changes a core part of their treatment regimens.

References

1. Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. N Engl J Med 1998; 339:861–867.
2. Heffler S, Levit K, Smith S, et al. Health spending growth up in 1999; faster growth expected in the future. Health Aff (Millwood) 2001; 20(2):193–203.
3. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998; 338:1650–1656.
4. Schwartz GE, Weiss SM. Proceedings of the Yale conference on behavioral medicine. Bethesda (MD): US Department of Health, Education, and Welfare. Public Health Service (NIH); 1978. Report No. 78-1424.
5. McGinnis JM, Foege WH. Actual causes of death in the United States [see comments]. JAMA 1993; 270:2207–2212.
6. Stampfer MJ, Hu FB, Manson JE, et al. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000; 343:16–22.
7. Fiore MC, Jorenby DE, Baker TB. Smoking cessation: principles and practice based upon the AHCPR Guideline, 1996. Agency for Health Care Policy and Research. Ann Behav Med 1997; 19:213–219.
8. Weintraub WS, Klein LW, Seelaus PA, et al. Importance of total life consumption of cigarettes as a risk factor for coronary artery disease. Am J Cardiol 1985; 55:669–672.
9. Hasdai D, Garratt KN, Grill DE, et al. Effect of smoking status on the long-term outcome after successful percutaneous coronary revascularization [see comments]. N Engl J Med 1997; 336:755–761.
10. Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. N Engl J Med 1985; 313:1511–1514.
11. Warner KE. Smoking out the incentives for tobacco control in managed care settings. Tob Control 1998; 7 Suppl:S50–S54.
12. Artaud-Wild SM, Connor SL, Sexton G, Connor WE. Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland. A paradox. Circulation 1993; 88:2771–2779.
13. Hu FB, Stampfer MJ, Manson JE, et al. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. BMJ 1998; 317:1341–1345.
14. Daviglus ML, Stamler J, Orencia AJ, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med 1997; 336:1046–1053.
15. Liu S, Stampfer MJ, Hu FB, et al. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr 1999; 70:412–419.
16. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999; 99:779–785.
17. Eckel RH, Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. Circulation 1998; 97:2099–2100.
18. Bouchard C, Tremblay A, Despres JP, et al. The response to long-term overfeeding in identical twins. N Engl J Med 1990; 322:1477–1482.
19. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA 1994; 272:205–211.
20. Mokdad AH, Serdula MK, Dietz WH, et al. The continuing epidemic of obesity in the United States. JAMA 2000; 284:1650–1651.
21. Gortmaker SL, Must A, Sobol AM, et al. Television viewing as a cause of increasing obesity among children in the United States, 1986–1990. Arch Pediatr Adolesc Med 1996; 150:356–362.
22. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. Lancet 2001; 357:505–508.
23. Hakim AA, Curb JD, Petrovitch H, et al. Effects of walking on coronary heart disease in elderly men: the Honolulu Heart Program. Circulation 1999; 100:9–13.
24. Anonymous. US Department of Health and Human Services. Healthy People 2000: national health promotion and disease prevention objectives. 1990; Washington: US Department of Health and Human Services. DHHS Publication No. (PHS) 91-50212.
25. Marmot MG, Bosma H, Hemingway H, et al. Contribution of job control and other risk factors to social variations in coronary heart disease incidence [see comments]. Lancet 1997; 350:235–239.
26. Diez-Roux AV, Northridge ME, Morabia A, et al. Prevalence and social correlates of cardiovascular disease risk factors in Harlem. Am J Public Health 1999; 89:302–307.
27. Shah SS, Cook DG. Inequalities in the treatment and control of hypertension: age, social isolation and lifestyle are more important than economic circumstances. J Hypertens 2001; 19:1333–1340.
28. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999; 99:2192–2217.
29. Kirkland SA, MacLean DR, Langille DB, et al. Knowledge and awareness of risk factors for cardiovascular disease among Canadians 55 to 74 years of age: results from the Canadian Heart Health Surveys, 1986–1992. CMAJ 1999; 161:S10–S16.
30. Schnall PL, Schwartz JE, Landsbergis PA, et al. A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. Psychosom Med 1998; 60:697–706.
31. Lynch J, Krause N, Kaplan GA, et al. Workplace demands, economic reward, and progression of carotid atherosclerosis. Circulation 1997; 96:302–307.
32. Karasek RA, Baker D, Marxer F, et al. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. Am J Public Health 1981; 75:694–705.
33. Johnson JV, Stewart W, Hall EM, et al. Long-term psychosocial work environment and cardiovascular mortality among Swedish men [see comments]. Am J Public Health 1996; 86:324–331.
34. Orth-Gomer K, Wamala SP, Horsten M, et al. Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study. JAMA 2000; 284:3008–3014.
35. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999; 99:2192–2217.
36. Gabbay FH, Krantz DS, Kop WJ, et al. Triggers of myocardial ischemia during daily life in patients with coronary artery disease: physical and mental activities, anger and smoking. J Am Coll Cardiol 1996; 27:585–592.
37. Frasure-Smith N, Lesperance F, Juneau M, et al. Gender, depression, and one-year prognosis after myocardial infarction. Psychosom Med 1999; 61:26–37.

38. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction [see comments]. Circulation 1998; 97:167–173.
39. Pfohl B, Sherman B, Schlechte J, Stone R. Pituitary-adrenal axis rhythm disturbances in psychiatric depression. Arch Gen Psychiatry 1985; 42:897–903.
40. Ziegelstein RC, Fauerbach JA, Stevens SS, et al. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. Arch Intern Med 2000; 160:1818–1823.
41. Frasure-Smith N, Lesperance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? Health Psychol 1995; 14:388–398.
42. Moser DK, Dracup K. Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? Psychosom Med 1996; 58:395–401.
43. Haines AP, Imeson JD, Meade TW. Phobic anxiety and ischemic heart disease. BMJ 1987; 295:297–299.
44. Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation 1994; 89:1992–1997.
45. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary heart disease. The Normative Aging Study [see comments]. Circulation 1994; 90:2225–2229.
46. Friedman M, Rosenman RH. Association of specific overt behavior pattern with blood and cardiovascular findings: blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. JAMA 1959; 169:1286–1296.
47. Miller TQ, Turner CW, Tindale RS, Posavac EJ. Reasons for the trend toward null findings in research on Type A behavior. Psychol Bull 1991; 110:469–485.
48. De Leon CFM, Kop WJ, de Swart HB, et al. Psychosocial characteristics and recurrent events after percutaneous transluminal coronary angioplasty. Am J Cardiol 1996; 77:252–255.
49. Koskenvuo M, Kaprio J, Rose RJ, et al. Hostility as a risk factor for mortality and ischemic heart disease in men. Psychosom Med 1988; 50:330–340.
50. Hecker MHL, Chesney MA, Blacks GW, Frautschi N. Coronary-prone behaviors in the Western Collaborative Group Study. Psychosom Med 1988; 50:153–164.
51. Dembroski TM, MacDougall JM, Costa PT, Grandits GA. Components of hostility as predictors of sudden death and myocardial infarction in the Multiple Risk Factor Intervention Trial. Psychosom Med 1989; 51:514–522.
52. Mittleman MA, Maclure M, Nachnani M, et al. Educational attainment, anger, and the risk of triggering myocardial infarction onset. The Determinants of Myocardial Infarction Onset Study Investigators. Arch Intern Med 1997; 157:769–775.
53. Siegman AW. From Type A to hostility to anger: reflections on the history of coronary-prone behavior. In: Siegman AW, Smith TW, editors. Anger, hostility, and the heart. Hillsdale (NJ): Lawrence Erlbaum; 1994. pp. 1–21.
54 Dimsdale JE, Pierce C, Schoenfeld D, et al. Suppressed anger and blood pressure: the effects of race, sex, social class, obesity, and age. Psychosom Med 1986; 48:430–436.
55 Gerin W, Christenfeld N, Schwartz AR. Effects of rumination and emotion regulation on autonomic arousal [abstract]. Psychophysiology 1998; 35:S8.
56 Kubzansky LD, Kawachi I, Spiro A, et al. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. Circulation 1997; 95:818–824.
57. Brosschot JF, Thayer JF. Anger inhibition, cardiovascular recovery, and vagal function: a model of the link between hostility and cardiovascular disease. Ann Behav Med 1998; 20:1–8.
58. Anonymous. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157:2413–2446.
59. Hjermann I, Velve BK, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. Lancet 1981; 2:1303–1310.
60. Glanz K. Nutrition education for risk factor reduction and patient education: a review. Prev Med 1999; 14:721–752.
61. Anonymous. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group [see comments]. Arch Intern Med 1997; 157:657–667.
62. Bandura A. Social foundations of thought and action: a social cognitive theory. Englewood Cliffs (NJ): Prentice-Hall, Inc.; 1986.
63. Robinson P, Wischman C, Del Vento A. Treating depression in primary care. Reno (NV): Context Press; 1996.
64. Ockene IS, Hebert JR, Ockene JK, et al. Effect of physician-delivered nutrition counseling training and an office-support program on saturated fat intake, weight, and serum lipid measurements in a hyperlipidemic population: Worcester Area Trial for Counseling in Hyperlipidemia (WATCH). Arch Intern Med 1999; 159:725–731.
65. Anonymous. American Heart Association. 2001 heart and stroke statistical update. Dallas (TX): American Heart Association; 2001.
66. Fries JF, Koop CE, Beadle CE, et al. Reducing health care costs by reducing the need and demand for medical services. The Health Project Consortium [see comments]. N Engl J Med 1993; 329:321–325.
67. Leigh JP, Fries JF. Health habits, health care use and costs in a sample of retirees. Inquiry 1992; 29:44–54.
68. Breslow L, Breslow N. Health practices and disability: some evidence from Alameda county. Prev Med 1993; 22:86–95.
69. McPhillips-Tangum C. Results from the first annual survey on addressing tobacco in managed care. Tob Control 1998; 7(Suppl):S11–S13.
70. Prochaska JO, Velicer WF, Rossi JS, et al. Stages of change and decisional balance for 12 problem behaviors. Health Psychol 1994; 13:39–46.
71. Dijkstra A, de Vries H, Roijackers J, van Breukelen G. Tailored interventions to communicate stage-matched information to smokers in different motivational stages. J Consult Clin Psychol 1998; 66:549–557.
72. Bandura A. Self-efficacy: the exercise of control. New York: W.H. Freeman and Company; 1997.
73. Cromwell J, Bartosch WJ, Fiore MC, et al. Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. Agency for Health Care Policy and Research [see comments]. JAMA 1997; 278:1759–1766.
74. Mechanic D, McAlpine DD, Rosenthal M. Are patients' office visits with physicians getting shorter? N Engl J Med 2001; 344:198–204.
75. Strosahl K. Integrating behavioral health and primary care services: the primary mental health care model. In: Blount A, editor. Integrated primary care: the future of medical and mental health collaboration. New York: W.W. Norton & Co.; 1998. pp. 139–166.
76. Bertagnolli A, Charlu M, Gordon M, Kent J. Re-engineering the primary care practice: the integration of health psychology and medicine. Ann Behav Med 1999; 21:S002.
77. Wegner EH, Austin BT, Davis C, et al. Improving chronic illness care: translating evidence into action. Health Aff (Millwood) 2001; 20(6):64–78.

Grand Rounds

Hypersensitivity Reactions to Drugs:

Evaluation and Management

Gillian M. Shepherd, M.D.

Abstract

Most hypersensitivity reactions to drugs occur within several weeks of administration; signs and symptoms are often consistent with known immune-mediated reactions, including anaphylaxis, rashes, fever, cytopenias and vasculitis. The culprit immune mechanisms range from immunoglobulin E antibody to T cells inducing apoptosis of keratinocytes, in the case of bullous exfoliative rashes. Many drugs induce reactions via altered hepatic metabolism, with production of reactive intermediates which induce a common syndrome of rash and fever plus variable types of other signs. Examples of this "reactive metabolite syndrome" include the rash and fever in HIV-positive patients given sulfamethoxazole and reactions to the aromatic anticonvulsants. With the notable exception of anaphylaxis and severe bullous exfoliative rashes, most immune reactions to drugs are not life-threatening and generally resolve once the drug is discontinued. The key is prevention. Specific immune testing is standardized only for penicillin. If test results are negative, however, the patient can tolerate all beta-lactam antibiotics. Of those patients with a positive penicillin skin test, only 2% develop reactions when given cephalosporins. Sulfa and quinolone antibiotics, and muscle relaxants, also frequently induce reactions. If there is a history of bullous rash, the patient should never again receive sulfa or quinolone, or related drugs. In other cases, a cautious graded challenge or desensitization can be done.

Vancomycin, protamine, and radiocontrast media induce non-immune reactions secondary to their irritant effects on vascular endothelium. Narcotic pain medications cause histamine release by binding to a specific receptor on mast cells in sensitive patients. In contrast to true immune reactions, most patients can receive these medications again, if they are pretreated and the drugs are given slowly. Angiotensin-converting enzymes, aspirin, and non- steroidal anti-inflammatory drugs induce adverse reactions by their effect on enzymes. Readministration usually results in repeat symptoms. It is possible to desensitize patients to aspirin. Some patients appear to develop similar adverse symptoms with multiple unrelated drugs. Although these cases present management problems, most patients can complete a therapeutic course of a vital drug, after careful review of the history, immune testing when possible, and graded challenge or desensitization.

Key Words: Drug allergy, drug hypersensitivity, allergy to antibiotics, drug rashes, hypersensitivity to beta-lactam antibiotics, hypersensitivity to sulfa drugs, mechanisms of drug allergy, signs and symptoms of drug hypersensitivity.

Introduction

Many patients experience hypersensitivity reactions to drugs. Only a small percent of these reactions are truly "allergic," i.e., the immune system specifically reacts to the drug, commonly with production of a specific antibody or sensitized T cells. Other reactions are the result of non-immune mechanisms, including altered hepatic metabolism, direct irritation of vascular endothelium, or interaction with enzymes.

A common problem encountered by physicians is the presentation of a patient on multiple drugs, with unpredictable signs or symptoms, thus raising the possibility of a hypersensitivity reaction. The first question that should be asked in this setting is whether the signs and symptoms are consistent with known immune-mediated reactions. These are discussed in detail below. If so, the next step is to evaluate the drugs the patient is taking. Most immune-mediated reactions to drugs occur within the first few weeks of administration. Since many patients, especially those who are hospitalized,

---

Clinical Associate Professor of Medicine, Weill Medical College of Cornell University, New York, NY.

Work originated from the Division of Allergy and Immunology, Department of Medicine, Weill Medical College of Cornell University, New York, NY.

Address all correspondence to Gillian M. Shepherd, M.D., 235 East 67 Street, Suite 203, New York, NY 10021; e-mail: gshepherd md@aol.com

Adapted from a Grand Rounds presentation to Department of Medicine, Mount Sinai School of Medicine, New York, NY, on December 12, 2000, and updated as of July 3, 2002.

are commonly on multiple drugs, several may be implicated as possible causes of the reaction. Patients also need to be questioned thoroughly about their intake of non-prescription products. One needs to know the propensity of these medications to stimulate the immune system. Drugs such as penicillin have chemically reactive metabolites which covalently bind to body proteins; these are more potent antigens than macrolide antibiotics, which have less chemically reactive metabolites, and other drugs.

Anaphylaxis

Common signs and symptoms of allergic drug reactions are noted in Table 1. The only life-threatening reaction other than toxic epidermal necrosis is anaphylaxis. Patients at risk of anaphylaxis have increased amounts of immunoglobulin E (IgE) antibody specific for the drug. IgE is attached to receptors on mast cells and basophils. Administration of the first therapeutic dose of the drug binds with this antibody; this induces an explosive release of mediators from the cell. The resultant signs and symptoms of anaphylaxis are predominantly due to histamine, although at least 15 other active chemicals are also released, such as prostaglandin D_2 and leukotriene C_4, which induce bronchoconstriction; cytokines IL-4 and 13, which increase IgE production; and tumor necrosis factor alpha (TNFα), a key cytokine in allergic inflammation. The clinical presentation is usually flushing, pruritus, urticaria, angioedema, bronchoconstriction and/or hypotension. Rarely, women may present with intense uterine cramping.

Epinephrine must be administered emergently to treat anaphylaxis. Appropriate fluids should be administered intravenously to restore intravascular volume. Antihistamines work by competitively binding to histamine receptors, thereby preventing manifestations of histamine release; they do nothing for an anaphylactic reaction, where histamine release has already occurred and symptoms are apparent. Steroids, likewise, are therapeutically ineffective for the immediate reaction.

The great majority of anaphylactic reactions occur within one hour of drug administration, while some of the reactions may occur later, within two hours (1). If a drug is subsequently administered according to its dosing interval, there should be no further risk of anaphylaxis beyond the first dose. Patients on beta-blocker (1) or angiotensin II inhibitors (2) may be at risk of more severe reactions.

Urticaria and Angioedema

Urticaria and angioedema are generally due to IgE antibody and can occur at any time during a course of drug administration. If a patient has sufficient IgE antibody prior to administration of the drug, urticaria and angioedema will commonly occur as part of anaphylaxis in the first one to two hours. In many cases, however, the patient does not have specific IgE antibody, or sufficient amounts of it, to induce an immediate reaction. In these cases, the immune system may turn on immediately, or days later, with stimulation of T cells inducing B cells to change to plasma cells and produce IgE. If the drug is administered on a regular schedule, the small initial amounts of new IgE will immedi-

TABLE 1

Signs and Symptoms Commonly Associated with Allergic Drug Reactions

Signs and Symptoms		Immune Mechanism
Anaphylaxis		IgE antibody
Urticaria and angioedema		IgE antibody
Rashes	– macular-papular	cytotoxic T cells kill keratinocytes expressing MHC II + drug
	– vesicular exfoliative	? CD8+ T cells induce lysis of keratinocytes
Fever		? release of cytokines
Immune complex reactions (rash, fever, arthralgias, myalgias, lymphadenopathy, nephritis, vasculitis)		IgG and IgM antibodies
Cytopenias		IgG and IgM antibodies

ately bind the drug, with resultant urticaria, starting slowly and increasing. If this occurs, the drug should be stopped, as IgE production will continue to increase.

Treatment of urticaria and angioedema consists of stopping the suspect drug and starting an antihistamine. The once-a-day preparations are usually effective. Occasionally, steroids may be necessary. Urticaria may persist beyond the half-life of the drug. This is probably due to the persistence of small amounts of tissue-bound drug.

Morbilliform Drug Rashes

The most common manifestation of an allergic reaction to a drug is a non-urticarial rash. Recent data suggest that there are two distinct types of rashes with different immune pathogenesis and prognosis: morbilliform or macular-papular and bullous. Morbilliform rashes are the most frequent immune reaction to drugs, occurring in approximately 2% of cases. Macules and papules of varying sizes, usually pruritic, occur symmetrically, commonly starting on the trunk, with eventual spread to the terminal extremities. Sometimes the face is spared. Onset varies from days to 1–2 weeks after initial administration of the drug. In some cases, the onset may occur after the drug has been discontinued. In these cases, residual tissue-bound drug can sometimes provide sufficient antigen to induce clinical symptoms for 1–2 weeks.

The pathogenesis is not clear, but most likely is mediated by cytotoxic T cells. Drugs can bind to major histocompatibility complex (MHC) class II antigens expressed on keratinocytes; T cells will then bind to the drug, thus inducing the T cell to release inflammatory cytokines, with resultant lysis of the keratinocytes (3, 4). There is limited research in this area, in part because it is clearly difficult to set up prospective studies, and because the rash, while uncomfortable, is rarely clinically significant. At worst, patients may experience epidermal peeling, similar to a bad sunburn. Treatment consists of stopping the drug, although sometimes it is possible to continue the treatment even when a rash occurs. This should only be done under the guidance of a physician familiar with drug rashes. If necessary, steroids (e.g., prednisone 30 mg on taper) may hasten resolution.

Uniquely, the aminopenicillins (e.g., ampicillin and amoxicillin) are associated with a high frequency of morbilliform rashes, up to 10% per course (5). If a patient has concurrent infectious mononucleosis, the frequency is 95% (6) to 100% (7). The mechanism is unknown, but there is no evidence of specific antibody. Immune responses to viral infections usually result in increased levels of interleukin 5 (IL5) which will upregulate expression of MHC class II antigens on keratinocytes. If the drug binds to MHC class II antigens, T cells can recognize the bound drug directly (4). Patients with a history of a rash coincident with an aminopenicillin have a higher frequency of certain major histocompatibility genes than do non-reactors (8). If the drug is continued, some rashes may clear spontaneously. In most cases, patients tolerate readministration of an aminopenicillin without incident (9). If the physician is sure that the past rash was morbilliform, patients can be rechallenged with any beta-lactam antibiotic. If, however, there is *any* question that the previous rash was urticarial, then there is the possibility of IgE involvement, and the patient must undergo skin testing, as discussed below, before any future beta-lactam antibiotic is administered.

Bullous Exfoliative Drug Rashes

The above-mentioned morbilliform rashes differ from blistering-exfoliative rashes, which appear to have a distinct immune pathogenesis. Although there is some disagreement, many physicians now categorize these rashes on a spectrum from minor to severe. Erythema multiforme minor is characterized by indurated lesions, at times bullous and often target shaped, with inner and outer red rings. Erythema multiforme major (also known as Stevens-Johnson syndrome) is the same rash, with systemic symptoms of fever and mucous membrane involvement, most commonly of the mouth or conjunctiva. Toxic epidermal necrolysis may be slightly different, as biopsies show necrosis of the "full" thickness of the epidermis, but most physicians consider it part of this spectrum, and it is generally defined as bullous rash involving more than 30% of the skin. The exact pathogenesis remains to be determined, but appears to involve activation of T cells which induce necrosis of epidermal cells (10). Sulfonamides account for the majority of drug-related episodes; however, it is a rare problem with a risk of 4.5 cases per million exposed persons per week (11). If there is any suspicion of a vesicular-exfoliative rash, the drug should be stopped immediately and the patient should be advised never to take that drug or one that is related.

Treatment of vesicular-exfoliative rashes is controversial. The mortality of toxic epidermal necrolysis used to approach 40%, as patients presented the same clinical management problems as severe burn patients, with loss of epidermis and subsequent fluid and infection problems. One paper suggested that steroid treatment is detrimental, since the mortality in the treated group was higher than in the untreated group (12). As a result, many physicians feel steroids are contraindicated for toxic epidermal necrolysis. Others, however, including this author, have used steroids with remarkable success for erythema multiforme major (13). Some anecdotal reports claim excellent results following the use of other immunosuppressants, including cyclosporin and tacrolimus. Most physicians now agree that steroids should be started at the first sign of a vesicular-exfoliative rash. High doses should be used initially, e.g., prednisone 60 mg, and then the dose should be tapered.

Drug Fever

Fever is also a manifestation of an immune reaction to a drug, but is often not considered in the differential diagnosis. If the suspect drug is stopped, the majority of patients will defervesce in 24 hours, and almost all by 48 hours (14). There is no characteristic fever pattern; shaking chills may occur, although there is a tendency for the patients to look better than one would expect with high fever from an infectious source. There is also no characteristic laboratory abnormality. The time between start of drug and onset of fever is variable, with a mean of 21 days and a median of 8 days (14). The immune mechanism is not clear, but is most consistent with release of pyrogenic cytokines, e.g., TNFα and IL1, from antigen-processing cells such as macrophages. Because there appears to be no other specific immune response, rechallenge appears safe, with immediate recurrent fever as the only manifestation (14).

Immune Complex Reactions

Drug allergy may also involve the production of specific IgG and IgM antibodies. The immune complexes of drug plus antibody, in slight antigen excess, can pass through the endothelial lining of blood vessels. In the tissue, they induce inflammation, in part because of complement activation. Depending on where they filter out, the clinical presentation can range from vasculitis with palpable purpura on the skin, to arthralgias, myalgias or nephritis. Complexes can also attach to blood cells, inducing cytopenias. Commonly, symptoms of immune complex disease appear after 7–10 days of drug administration. It takes that long for adequate amounts of antibody to be formed in order to create complexes of slight antigen excess. Generally, it is a self-limiting problem; if the drug continues to be administered, antibody production continues and complexes become larger, with antibody excess. The larger complexes are too big to pass through endothelial lining and are cleared by the reticular endothelial system. If treatment is necessary, prednisone 30 mg or equivalent, tapered pending symptoms, is usually sufficient.

Drug Hypersensitivity Due to Altered Hepatic Metabolism: The Reactive Metabolite Syndrome

Other reactions to drugs do not involve the classic mechanisms discussed above, but are a result of the altered hepatic metabolism of drugs, with production of reactive intermediate metabolic products (15). Examples of reactions due to altered hepatic metabolism include: the rash and fever associated with sulfamethoxazole in HIV-positive patients (16, 17); cefaclor and probably cefprozil "serum-sickness-like" reactions (18, 19); the fever, rash and lymphadenopathy reactions to the aromatic anticonvulsants which produce arene oxide (e.g., phenytoin, carbamazepine or phenobarbital) (20); and "lupus-like" reactions from prolonged treatment with procainamide (21).

Most drugs are metabolized in the liver by acetylation, hydroxylation, or glucuronidation, with the production of nontoxic metabolites. Some drugs, however, are selectively or partially metabolized by the cytochrome P450 system, with the production of reactive intermediates, such as sulfamethoxazole-hydroxlyamine in the case of sulfamethoxazole. Most reactive metabolites are rapidly detoxified by enzymes, which may not be as active or efficient in patients who develop adverse reactions. In the case of the anticonvulsants, the toxic intermediate products are arene oxide metabolites. Anticonvulsant hypersensitivity syndrome seems to be associated with an inherited deficiency of epoxide hydrolase, the enzyme responsible for metabolizing these intermediate products (20). Some first-degree relatives of patients who have had reactions to cefaclor and the aromatic anticonvulsants also have altered hepatic metabolism of the same drugs (22). Patients should therefore be asked if relatives have experienced adverse reactions to these or other drugs. In the case of HIV-positive patients, some have been noted to be deficient in glutathione, which enhances metabolism of the reactive metabolite of sulfa (23). Some patients may be slow acetylators; therefore, an increased amount of drug is metabolized instead by the cytochrome system. This has been noted in 90% of HIV patients versus 55% of age-matched controls (24).

Six cytochrome isoenzymes are responsible for most drug metabolism. These are cytochromes 1, 2, and 3 with the respective isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. 3A4 is the most abundant and accounts for the largest percent of drug metabolism (25). Theoretically, a patient might have abnormal metabolism via one isoenzyme and therefore react to other drugs metabolized by this route. Interaction between drugs which competitively bind, inhibit, or induce the same P450 isoenzymes may also contribute to reactions (25). Grapefruit juice inhibits intestinal (but not hepatic) cytochrome 3A4 and may increase serum levels of some drugs such as statins (26).

The reactive metabolites may induce adverse reactions by either directly causing cell injury, inducing apoptosis, or acting via an as yet undefined immune reaction. To date, there is no evidence that a specific antibody is involved in these reactions.

Typically, the treatment consists of stopping the drug. An HIV-positive patient who has had a rash and fever with sulfamethoxazole can usually be rechallenged without an adverse event. This success may be due to fluctuating differences in oxidative metabolism, or reductive capacity, at various stages of AIDS. With other drugs, rechallenge will usually result in repeat symptoms, occasionally severe. In most cases, these reactions are drug specific. Structurally similar drugs are often tolerated, e.g., loracarbef in patients who had a reaction to cefaclor (27).

Prevention

The above discussion has focused on diagnosis and management of immune-mediated drug reactions, but the primary goal should be prevention. This means identifying the patient who is at risk of an immune reaction if given a particular drug. Unfortunately, the only reliable predictive test at present is an intracutaneous or intradermal skin test, and this is only standardized for penicillin and insulin. Skin testing for other drugs is not standardized, in part because relevant antigens are not known and because many drugs induce nonspecific irritant reactions. Radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA) tests (looking for specific IgE in serum) are less sensitive than skin testing, and in almost all cases the relevant drug antigens are not available for testing, generally because they are not known. *In vitro* or patch testing to detect other types of immune reactivity is either not predictive or not standardized.

One of the most common problems related to drug allergy concerns the patient with a history of reacting to a specific drug, who now ideally needs therapy with that drug or another in the same class. In this case, the first step is to get a detailed history of the original reaction. In some cases, it is obvious that the symptoms were not immune mediated; in some, there may be concern because of a family history of a reaction. A tendency to allergic disorders is inherited, but not a tendency to specific drug reactions, although this has recently been challenged (28). As noted above, there are very few definitive diagnostic tests to help clarify this situation. The goal is to identify the patient with sufficient IgE antibody who might be at risk of life-threatening anaphylaxis if given the drug. Almost all immune reactions that develop later in the course of drug administration are not life-threatening and can generally not be predicted. If the allergy cannot be defined adequately from history and available testing, there are three other possible approaches.

1. Use an alternate antibiotic, if possible. This is the safest approach.
2. Administer the drug initially via a "graded challenge," i.e., do cautious test dosing when there is a suspect history, but there is either no specific diagnostic test or no evidence of IgE antibody. Small incremental doses are given, under medical supervision. For example, give 1/100 of the therapeutic dose by the indicated route; if there is no reaction in one hour, proceed to 1/10 of the therapeutic dose. Likewise, if no reaction in one hour, proceed with the full dose. If there is a significant history or if the patient is medically unstable, one might elect to start with 1/1000 of the therapeutic dose. Once the first therapeutic dose is tolerated, anaphylaxis with subsequent doses given regularly is extremely unlikely.

3. "Desensitize" the patient if there is a history or testing suggestive of an IgE reaction to a drug and the patient currently needs that drug. The only absolute indication to do this is a patient with a positive skin test to penicillin who is pregnant and has syphilis. Very small incremental doses of the drug are administered IV or po every 20–30 minutes. The mechanism appears to be gradual absorption of specific IgE with incremental amounts of drug. Histamine release will probably occur gradually, but the sudden release of massive quantities is avoided. It is a potentially dangerous procedure and should be done in a monitored setting, by a physician capable of treating anaphylaxis. On average, it takes several hours.

Penicillin Allergy

Many patients claim a history of penicillin allergy; however, when these patients undergo specific penicillin skin testing, only approximately 15% have positive skin tests indicating the presence of IgE in response to penicillin at the time of testing (29). The remainder have either lost the allergy over time or never had a true allergic reaction to penicillin; for example, some may have had viral exanthems. The reagents and techniques of penicillin skin testing are detailed by Bernstein et al. (30). The reagents should include the major determinant of penicillin (benzyl penicilloyl), commercially available as Pre Pen, and a mix of minor determinants which is not commercially available, or penicillin G as a substitute. Testing for serum levels of penicillin-specific IgE via a RAST or ELISA assay is available only for the major determinant and is not adequately sensitive to detect potential anaphylactic sensitivity.

A negative penicillin skin test means there is a 99% chance the patient will not have an IgE-mediated reaction to penicillin within 24 hours of administration (31). The 1% of patients who did react during clinical trials had minor symptoms, with no documented episodes of anaphylaxis. Because it is impossible to predict which patients will develop an immune reaction once they are exposed to the drug, this testing is not predictive of the chance of developing an IgE-mediated reaction occurring beyond 24 hours, or a T cell or other immune-mediated reactions, such as a morbilliform rash. However, with the possible exception of toxic epidermal necrolysis, none of these later immune reactions are life-threatening.

Penicillin skin testing should be considered for any patient with a history of penicillin allergy who ideally needs a beta-lactam antibiotic for therapy. This should be done particularly when the alternate antibiotic is vancomycin. Generally, patients with a history of penicillin allergy are placed on vancomycin more commonly than are non-allergic patients (32). This practice is undoubtably contributing to the problem of vancomycin-resistant microbial strains. If these patients are skin tested, approximately 85% would be able to tolerate a beta-lactam drug.

All penicillin derivatives should be considered antigenically cross-reactive. A history of allergy to penicillin and a negative penicillin skin test predicts that the patient is able to receive any "cillin" derivative (30). Rarely, patients may have isolated immune reactions to side chains of the aminopenicillins (ampicillin and amoxicillin). This sensitivity cannot be detected by penicillin skin testing, but may be detected by skin testing with the aminopenicillins (33). Approximately 5–10% of patients receiving aminopenicillins develop a morbilliform rash. This is discussed in detail in the section on morbilliform rashes. Patients with a history of such a rash should avoid further aminopenicillins, although, if necessary, most patients can tolerate later re-exposure without incident.

Cephalosporin Allergy

Most physicians are not sure whether cephalosporins can be given to a patient with a history of penicillin allergy. The literature does not provide a definitive recommendation, since most reports are based only on history, without recording the results of specific skin testing. Penicillins and cephalosporins share the same beta-lactam ring structure. This ring is the site of metabolism, with production of antigenic determinants in the case of penicillin. This potential cross-reactivity, however, does not appear to be a significant clinical problem, as noted below. Table 2 details 468 patients with a history of allergy to penicillin and negative skin tests to penicillin; all but 3 (0.6%) tolerated subsequent cephalosporins (34, 35, personal communication). The three reactions were non-anaphylactic. Therefore, regardless of the history, if there is no evidence of an IgE response to penicillin by skin testing, such a patient should be able to tolerate a cephalosporin.

TABLE 2

Patients with a History of Penicillin Allergy and Negative Skin Tests to Penicillin Challenged with Cephalosporins

Reference	Patients Challenged	Reactions Within 24 Hours	Skin Test Reagents
Solley et al. (35)	151	2	Penicilloyl MDM*
Shepherd and Burton (34)	159	1 (itchy eye)	Penicilloyl Penicillin G
Shepherd (unpublished)	158	0	Penicilloyl Penicillin G
Total	468	3 (0.6%)	

*MDM = minor determinant mix consisting of penicillin G and penicilloate

Even if patients have a positive skin test to penicillin, the overwhelming majority still tolerate a cephalosporin, as shown in Table 3. Since 1980, 160 such patients have been reported with three anaphylactic reactions (2%), only one of whom was in the U.S. (29, 34–39). Prior to 1980, the incidence was higher (40). This may reflect more early use of first-generation cephalosporins, some of which were contaminated with trace amounts of penicillin. There may have been cross-reactive IgE response to side chains; most patients received cephalothin or cephaloridine, both of which share a side chain that is similar to penicillin (40). Later cephalosporins have bulkier side chains. Potentially, these may stereochemically block IgE from binding to the beta-lactam ring. Patients can also make antibody to a side chain and not to the beta-lactam ring; as a result, they will only react to cephalosporins or penicillins with the same side chain (41). Based on the above, if a patient with a history of penicillin allergy is given a cephalosporin without further evaluation, the chance of a reaction is less than 1%. For example, for every 100 patients with a history of penicillin allergy, only approximately 15 will have positive skin tests. If the positive-skin-test patients are given a cephalosporin, fewer than 2% will react, i.e., fewer than one patient out of the original 100.

If patients have a history of allergy to penicillin and need a cephalosporin, they should undergo penicillin skin testing. If negative, they can receive a cephalosporin with less than a 1% chance of developing a non-life-threatening reaction (34, 35). If positive, they should either receive an alternate drug or undergo a cautious graded challenge with the cephalosporin under medical supervision. The chance of anaphylaxis is less than 2%, but it is still possible.

Monobactam and Carbapenem Allergy

The monobactam, aztreonam, does not seem to cross react with other beta-lactam drugs (41, 42). However, imipenem, a carbapenem, should be considered potentially cross-reactive with penicillin based on skin test data (43).

Sulfonamide Allergy

IgE-mediated reactions to sulfa are uncommon, but diagnosis is hampered, as there is no standardized skin test reagent. The most common immune-mediated reaction is rash. Sulfa antimicrobials have been estimated to induce 70% of cases of drug-induced bullous rashes (11). Immune reactions to sulfonamides are thought to be directed to the sulfur atom attached to an aromatic amine. Drugs with this configuration, which potentially may be cross reactive, are listed in Table 4. They include all the sulfa antimicrobials and the cyclo-oxygenase 2 (COX II) inhibitor, celecoxib. The other COX II inhibitors do not have a sulfa tail. Although chemically distinct, dapsone has induced rash in 7% (44) to 20% (45) of HIV patients with a history of rash from sulfamethoxazole. The sulfonylurea oral hypoglycemic drugs, thiazide diuretics and carbonic anhydrase inhibitors, have sulfa moieties; although there is very limited data, there is no evidence to date of immune reactions to these drugs in patients with a history of sulfa sensitivity. Because of the limited data, however, it may be prudent to use alternate treatment where possible, especially for any patient with a history of a bullous rash. This is an

TABLE 3

Patients with a History of Penicillin Allergy and Positive Skin Tests to Penicillin Challenged with Cephalosporins since 1980

Reference	Patients Challenged	Reaction Within 24 Hours	Skin Test Reagent	Comments
Solley et al. (35)	27	0	Penicilloyl MDM*	
Rohr (36)	62	1	Penicilloyl MDM*	Mild urticaria / bronchospasm
Van Arsdel et al. (37)	6	0	Penicilloyl MDM*	
Blanca et al. (38)	19	2	Penicilloyl MDM*	Anaphylaxis to cefamandole
Shepherd (29)	3	0	Penicilloyl MDM*	
Shepherd and Burton (34)	9	0	Penicilloyl	
(Shepherd unpublished)	6	0	Penicillin G	
Macy (39)	28	0	Penicilloyl MDM*	
TOTAL	160	3 (2%)		

*MDM = minor determinant mix

issue with acetazolamide, frequently prescribed for high-altitude symptom prophylaxis or treatment. Although there is no documentation of "cross reaction" with sulfa, patients are going to take acetazolamide in remote areas with limited access to medical care. It may be prudent to have these patients test dose the medication before leaving, although it can be argued that this could stimulate a later immune reaction.

HIV-positive patients who take trimethoprim-sulfamethoxazole prophylaxis for pneumocystis develop a morbilliform rash and fever 10–50 times more frequently than do non-HIV-infected patients (46). This is secondary to hepatic production of reactive metabolites of sulfamethoxazole, as discussed in the section on altered hepatic metabolism. In 95% of cases, patients can tolerate readministration (47). If the mechanism of the rash is T cell binding and killing of keratinocytes expressing MHC class II antigen plus bound drug, a possible pathogenesis is that viral infections increase interferon (INF) gamma, which increases MHC class II expression on keratinocytes and thus leads to increased T cell binding (4). As CD4 counts decrease, the frequency of rashes also decreases (48). When the problem was first identified, multiple papers reported success readministering the sulfa drug slowly over weeks; subsequent publications reported success with progressively shorter protocols. The most recent protocol, with the highest success rate, gives the drug over six hours (47). This is a "graded challenge," not a "desensitization"; the only immune mechanism that can be manipulated in six hours is that of IgE antibody, and there is no evidence of IgE in these cases. If an HIV-positive patient has had a history of rash and fever with trimethoprim and sulfamethoxazole, it may be prudent to wait several weeks before rechallenge. The drug can then be given in incremental doses over several hours. It is also important to continue treatment if rash and fever recur (7). If there is any history suggestive of a bullous rash, readministration is contraindicated. Likewise, if the past reaction is other than rash and fever, for example, hepatitis or cytopenias, patients ideally should not be rechallenged.

TABLE 4
Sulfonamides and Other Derivatives

Drugs	Brand Names
Sulfonamide Antibiotics	
sulfamethoxazole	Bactrim, Septra
sulfisoxazole	Pediazole
sulfamethizole	Urobiotic
sulfacetamide	Blephamide eye drops Sulfacet-R lotion
mafenide acetate	Sulfamylon cream
sulfanilamide	AVC cream or suppositories
sulfathiazole, sulfabenzamide, sulfacetamide	Sultrin triple cream
sulphasalazine	Azulfidine
Non-steroidal Anti-inflammatory	
celecoxib	Celebrex
***Carbonic Anhydrase Inhibitors**	
acetazolamide	Diamox
dichlorphenamide	Daranide
dorzolamide, brinzolamide	Trusopt, Cosopt, Azopt
***Sulfonylurea Oral Hypoglycemics**	
glyburide	DiaBeta
glipizide	Glucotrol
chlorpropramide	Diabenase
tolazamide	
***Diuretics**	
thiazides	HydroDIURIL, Diuril, Enduron, Microzide
others	Furosemide

*Although these drugs contain sulfa in their chemical structure, there are no reports of patients with a history of sulfa antibiotic sensitivity subsequently reacting to one of these.

Allergy to Quinolone Antibiotics

Quinolone antibiotics induce nonspecific histamine release; for example, an intradermal injection of as little as 0.02 mL of a 0.0001 mL concentration will commonly induce a hive. For this reason, specific skin testing generally cannot be done. Additionally, there are no *in-vitro* assays for specific IgE responses to quinolones. There are several reports of anaphylactic reactions with ciprofloxacin, many with first known exposure, which strongly suggests non-immune-mediated histamine release (49). HIV-positive patients may be at greater risk of reactions (49). The author is aware of several cases where such patients subsequently had a comparable reaction to another quinolone. For these reasons, if a patient has a history compatible with anaphylaxis or significant urticaria from one quinolone, until further diagnostic testing is available, that patient should avoid all quinolones.

If the history of adverse reaction is a morbilliform rash, it is unclear whether the patient can be rechallenged. This is a less common situation. In all of these cases, an alternate drug should be given, if possible. If a quinolone must be administered in this case, the patient should undergo a graded challenge, as described above. There is one report of a successful "desensitization" to ciprofloxacin in a patient who had had a prior reaction (50).

Allergy to Muscle Relaxants

Allergic reactions often result from muscle-relaxant drugs administered during anesthesia (51), particularly from suxamethonium, gallamine, vecuronium, and pancuronium (52). Most are presumed to be mediated by specific IgE antibody, although only a small percent of patients with a positive skin test develop symptoms with exposure (53). This category of drugs may also be capable of non-antibody-mediated activation of basophils, with resultant release of histamine.

Allergy to Local Anesthetics

Despite the perception that many patients are allergic to local anesthetics, true IgE-mediated reactions are extremely rare; there is disagreement as to whether any well-documented case has been reported (54). Reported reactions are most likely due to other reasons, including hyperventilation, vasovagal reactions, numbness of the pharynx from extravasated anesthetic, or inadvertent intravascular injection of epinephrine (added to most local anesthetics to vasoconstrict the area). Regardless of the history, the easiest approach is to pick an alternate anesthetic, as listed in Table 5. The patient should undergo skin prick and intradermal skin tests with the alternate, using incremental doses, depending on the history, followed by a subcutaneous challenge with approximately 0.2 mL. (Dental vials have 1.8 mL.) If no reaction ensues, the patient will not react significantly when given ten times the dose. Ideally, testing should be done with local anesthetics without epinephrine, as skin blanching may occur, which can be misinterpreted as an immune reaction. Then a note needs to be written documenting that the patient has successfully tolerated the local anesthetic. Although there is almost no concern regarding an IgE-mediated reaction, the

TABLE 5
Common Local Anesthetics

Generic Name (Brand Name)
procaine (Novocain)
bupivacaine (Marcaine, Sensorcaine)
lidocaine (Xylocaine)
mepivacaine (Carbocaine, Polocaine)
prilocaine (Citanest)
benzocaine — in topical preparations and some sore throat lozenges
pramoxine — in topical preparations
proparacaine — (Alcaine, Ophthetic) eye drops

above needs to be done to reassure the patient and the referring dentist or physician.

Anaphylactoid or Non-immune-Mediated Drug Reactions

A variety of drugs cause reactions that are clinically indistinguishable from true allergic reactions. In these cases, however, the specific immune system is not involved. The reactions are partly related to the dose and rate of infusion. In contrast to true IgE-mediated reactions, life-threatening reactions with minuscule amounts of drug are very unlikely. For this reason, many of these drugs can be readministered after pretreatment and appropriate dosing. Vancomycin, protamine and opioids induce symptoms by non-immune-mediated histamine release, aspirin and non-steroidal anti-inflammatory drugs via enzyme blockade. Although not technically a drug, radiocontrast media is included here as it also induces nonspecific histamine release in sensitive individuals.

Vancomycin

Administration of vancomycin is commonly associated with "the red man syndrome" characterized by flushing, erythema, and pruritus, characteristically in the upper extremities and torso. Hypotension can occur. These symptoms appear to be due to nonspecific histamine release associated with rapid infusions. If the drug is given again to adults with an infusion rate of one gram over two hours (instead of the usual one hour), most patients tolerate readministration (55). Rarely, the infusion needs to be slower. Patients may also be helped by pretreatment with an antihistamine.

Vancomycin is also associated with morbilliform rashes. These are more common with prolonged courses and probably are immune mediated. Management is discussed in the section on morbilliform rashes.

Protamine

Protamine is commonly used to reverse heparin anticoagulation during cardiac and other procedures. As with vancomycin, IV infusion can trigger non-immune-mediated histamine release, with resultant symptoms of anaphylaxis (56). Reactions to protamine, however, are up to 25 times more frequent in diabetic patients taking NPH (neutral protamine Hagedorn) insulin (57). It is unclear whether this is immune mediated, but it is of concern, as diabetic patients frequently require cardiac procedures. At present there is no accepted substitute. Several reference laboratories can detect IgE or IgG specific for protamine. If the results are positive, a patient is at increased risk of anaphylaxis. It is unclear whether pretreatment with antihistamine and possibly steroids is protective. In all cases where an NPH-dependent diabetic patient requires protamine, it should be given as slowly as possible, with close monitoring of vital signs.

Opioids / Narcotic Pain Medications

Morphine, meperidine and codeine are nonspecific histamine liberators. They bind to a specific receptor on mast cells, with resultant histamine release and the clinical presentation of pruritus and urticaria. More severe reactions are very unusual. The effect is somewhat dose dependent and is perhaps associated with the potency of the drug. If a patient has severe symptoms, ideally a non-opioid pain medication should be given, such as ketorolac tromethamine (Toradol®), but no one should be denied narcotic analgesics because of concern about anaphylaxis. Patients with this history should undergo a graded challenge. Most will tolerate smaller doses, and many are helped by coincident antihistamines.

Aspirin and Non-steroidal Anti-inflammatory Drugs

These drugs are associated with aspirin-sensitive respiratory disease, a triad of rhinosinusitis, nasal polyps and asthma (58). Approximately 30–40% of adults with asthma and rhinosinusitis are sensitive to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) (59). If exposed, they develop symptoms ranging from increased nasal congestion to severe asthma and anaphylaxis. Rarely, patients have anaphylactic sensitivity to aspirin and NSAIDs without the triad symptoms. The mechanism may be blockade of the cyclo-oxygenase enzyme with resultant overproduction of leukotrienes, especially LT3, 4 and 5. These are potent bronchoconstrictors. This sensitivity appears to be related only to blocking the COX I isoform of the enzyme, as patients with aspirin-induced asthma have been shown to tolerate COX II inhibitors (60). Why only a subset of patients have this sensitivity to aspirin and NSAIDs is not known. Unfortunately, it is a class effect, but some drugs induce more severe symptoms. This appears to be related to the strength of the enzyme blockade. Patients may tolerate weaker COX I inhibitors, such as acetaminophen or salsalate, but usually these do not provide adequate symptom relief.

There is no specific diagnostic test to identify sensitive patients, or to determine which, if any, NSAIDs a patient may tolerate. At present, this can only be done by a very cautious graded challenge, following pulmonary spirometry, by a physician with experience in the treatment of anaphylaxis. In many cases, patients will tolerate low doses, but develop asthma with higher concentrations. In select cases, it is possible to "desensitize" patients with severe triad symptoms to aspirin and maintain them on a regular daily dose. This has been associated with clinical improvement in these patients (61). One study documented successful oral challenge-desensitization over several hours in 11 patients with aspirin- or NSAID-induced angioedema and urticaria (62). Leukotriene inhibitors blocking lipoxygenase activating factor or LT4 receptors have also helped some of these patients, but have not been shown, so far, to block specific aspirin or NSAID sensitivity.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are associated with a cough in up to 25% and angioedema in 0.1–0.2% of treated patients (63). The precise mechanism is not known, but is likely to be related to alterations in kinin generation in sensitive patients. ACE inhibitors block an enzyme responsible for kinin metabolism. There is no evidence of specific immune mediation. The angioedema can be potentially life threatening; therefore, any patient with angioedema should be checked to see if he or she is taking an ACE inhibitor. The onset of angioedema reactions is variable, but usually occurs after one month or more of treatment (63).

Radiocontrast Media

Histamine-mediated reactions to radiocontrast media are common. There is no evidence of specific immune mediation. Reactions appear to be related to intravascular injections of hyperosmolar material. The specific mechanism is not known; possible mechanisms include activation of blood basophils or complement with production of the fifth component of complement (C5a), which is capable of directly releasing histamine from mast cells via a specific complement receptor (64). Patients who react appear to have more reactive vascular endothelium. Reactions seem to occur only with intravascular administration. Newer "non-ionic / low-osmolar" preparations are associated with a lower incidence of reactions, but the frequency of severe reactions is similar to that with hyperosmolar agents (65). Repeat reaction can be prevented by pretreatment with steroids and antihistamines, as noted in Table 6 (66). Patients at risk of a reaction to radiocontrast media should be off beta-blockers (67) and possibly inhibitors of angiotensin II (2) before the procedure. Recent reports suggest that, rarely, some patients may develop delayed rashes (68).

Reactions to Excipients in Drugs

All drugs have multiple excipients added. These may include preservatives and coloring agents. For example, a 1.25-mg tablet of Premarin® (conjugated estrogens) has 16 excipients in addition to estrogen. Allergic reactions to the additives are very unusual, but may possibly occur to propylene glycol, parabens, and thimerosol. If this is suspected, the patient should be tested with different drugs containing

TABLE 6
Pretreatment Regimen to Block Repeat Reactions to Radiocontrast Media

prednisone 50 mg po: 13, 7 and 1 hour before the procedure.
diphenhydramine 50 mg IV or IM: one hour before the procedure.
Patients at risk should ideally be off beta-blockers and angiotensin II receptor antagonists at the time of the procedure.

Adapted from Reference 66.

the same additives. IgE-mediated reactions have been described with gelatin, used as a stabilizer in some vaccines for measles, mumps and rubella (MMR), diphtheria, pertussis, and tetanus (DPT) and varicella, as well as for some preparations of erythropoietin. With one exception, all reported cases are from Japan (69).

Multiple Drug Allergy

It has been reported that 18 – 27% of patients who react to one drug, especially an antimicrobial, have an increased frequency of similar subsequent reactions to chemically distinct drugs (70). A more recent study, however, found no difference in reactions to non-beta-lactam antibiotics between patients with documented allergy to penicillin and those with no evidence of prior immunologic drug reactions (71). In all cases where patients report adverse reactions to multiple drugs, a careful history will usually limit the possible offending drugs. Many patients mistakenly believe that an increased sensitivity to known side effects is caused by allergy. In some cases specific skin testing may help to differentiate these responses. If questions remain and the patient needs a specific drug, a graded challenge or desensitization can be done.

Summary

Hypersensitivity reactions to drugs may not be readily apparent. The key is to suspect this diagnosis in any patient with unanticipated signs or symptoms within several weeks of starting a new medication. With the notable exceptions of anaphylaxis and severe blistering exfoliative rashes, most immune-mediated reactions to drugs are not life-threatening and generally resolve once the drug is discontinued.

References

1. Bochner BS, Lichtenstein LM. Current concepts: anaphylaxis. N Engl J Med 1991; 324:1785 – 1790.
2. Kemp SF, Lieberman P. Inhibitors of angiotensin II: potential hazards for patients at risk for anaphylaxis. Ann Allergy Asthma Immunol 1997; 78:527 – 529.
3. Yawalkar N, Shrikhande M, Hari Y, et al. Evidence for a role for IL5 and eotaxin in activating and recruiting eosinophils in drug-induced cutaneous eruptions. J Allergy Clin Immunol 2000; 106:1171 – 1176.
4. Pichler WJ, Yawalkar N. Pathophysiology of drug-induced exanthems. ACI International 2001; 12/4:166 – 170.
5. Hoigne R, Sonntag R, Zoppi M. et al. Occurrence of exanthems in relation to aminopenicillin preparations and allopurinol [letter]. N Engl J Med 1987; 316:1217.
6. Pullen H, Wright N, Murdock JM. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. Lancet 1969; 2:1176 – 1178.
7. Kerns DL, Shera JE, Go S, et al. Ampicillin rash in children: relationship to penicillin allergy and infectious mononucleosis. Am J Dis Child 1973; 125:187 – 190.
8. Romano A, Santis A, Romito A, et al. Delayed hypersensitivity to aminopenicillins is related to major histocompatibility complex genes. Ann Allergy Asthma Immunol 1998; 80:42 – 47.
9. Bierman CW, Pierson WE, Zeitz SJ, et al. Reactions associated with ampicillin therapy. JAMA 1972; 220:1098 – 1100.
10. Leyva L, Torres MJ, Posadas S, et al. Anticonvulsant-induced toxic epidermal necrolysis: monitoring the immunological response. J Allergy Clin Immunol 2000; 105:157 – 165.
11. Roujeau J-C, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333:1600 – 1607.
12. Halebian PH, Corder VJ, Madden MR, et al. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg 1986; 204:503 – 512.
13. Tripathi A, Ditto AM, Grammer LC, et al. Corticosteroids therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. Allergy Asthma Proc 2000; 21:101 – 105.
14. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. Ann Intern Med 1987; 106:728 – 733.
15. Knowles SR, Uetrecht J, Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndrome. Lancet 2000; 356:1587 – 1591.
16. Shear NH, Spielberg SP, Grant DM, et al. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. Ann Intern Med 1986; 105:179 – 184.
17. Rieder MJ, Uetrecht J, Shear NH, et al. Diagnosis of sulfonamide hypersensitivity reactions by in-vitro "rechallenge" with hydroxylamine metabolites. Ann Intern Med 1989; 110:286 – 289.
18. Kearns GL, Wheeler GJ, Childress SH, Lefzig LG. Serum sickness reactions to cefaclor: role of hepatic metabolism and individual susceptibility. J Pediatr 1994; 125:805 – 811.
19. Lowery N, Kearns GL, Young RA, Wheeler G. Serum sickness-like reactions with cefprozil therapy. J Pediatr 1994; 125:325 – 328.
20. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. Arch Intern Med 1995; 155:2285 – 2290.
21. Jiang X, Khursigara G, Rubin RL. Transformation of lupus-inducing drugs to cytotoxic products by activated neutrophils. Science 1994; 266:810 – 813.
22. Gennis MA, Vemuri R, Burns EA, et al. Familial occurrence of hypersensitivity to phenytoin. Am J Med 1991; 91:631 – 634.
23. Buhl R, Jaffe HA, Holroyd KJ, et el. Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. Lancet 1989; 334:1294 – 1298.
24. Rieder MJ, Shear NH, Kanee A, et al. Prominence of slow acetylator phenotype among patients with sulfonamide hypersensitivity reactions. Clin Pharmacol Ther 1991; 49:13 – 17.
25. Gregg CR. Drug interactions and anti-infective therapies. Am J Med 1999; 106:227 – 237.
26. Greenblatt DJ, Patki KC, von Moltke LL, Shader RI. Drug interaction with grapefruit juice: an update. J Clin Psychopharmacol 2001; 21:357 – 359.
27. Kearns GL, Wheeler JG, Reider MJ, Reid J. Serum sickness-like reaction to cefaclor: lack of in vitro cross-reactivity with loracarbef. Clin Pharmacol Ther 1998; 63:686 – 693.
28. Kurtz KM, Beatty TL, Adkinson NF Jr. Evidence for familial aggregation of immunologic drug reactions. J Allergy Clin Immunol 2000; 105:184 – 185.
29. Shepherd G. Allergy to beta-lactam antibiotics. In: Van Arsdel PP, editor. Immunology and allergy clinics of North America. Philadelphia: WB Saunders; 1991:611 – 633.
30. Bernstein IL, Gruchalla RS, Lee RE, et al., editors. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy Asthma Immunol 1999; 83:665 – 700.

31. Sogn DD, Evans R III, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases collaborative clinical trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Intern Med 1992; 152:1025–1032.
32. Solensky R, Earl HS, Gruchalla RS. Clinical approach to penicillin allergic patients: a survey. Ann Allergy Asthma Immunol 2000; 84:329–333.
33. Romano A, Torres MJ, Fernandez J, et al. Allergic reactions to ampicillin: studies on the specificity and selectivity in subjects with immediate reactions. Clin Exp Allergy 1997; 27:1425–1431.
34. Shepherd GM, Burton DA. Administration of cephalosporin antibiotics to patients with a history of allergy to penicillin [abstract]. J Allergy Clin Immunol 1993; 91:262.
35. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin test reagents. J Allergy Clin Immunol 1982; 69:238–244.
36. Rohr AS. Cephalosporins, pp. 209–210. In: Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987; 107:204–215.
37. Van Arsdel PP, Martonick GJ, Johnson LE, et al. The value of skin testing for penicillin allergy diagnosis. West J Med 1986; 144:311–314.
38. Blanca M, Fernandez J, Miranda A, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunological studies. J Allergy Clin Immunol 1989; 83:381–385.
39. Macy E. Elective penicillin skin testing and amoxicillin challenge: effect on outpatient antibiotic use, cost, and clinical outcomes. J Allergy Clin Immunol 1998; 102:281–285.
40. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. Ann Allergy Asthma Immunol 1995; 74:167–170.
41. Adkinson NF, Jr. Immunogenicity and cross-allergenicity of aztreonam. Am J Med 1990; 88:(Suppl 3C):12s–16s.
42. Saxon A, Hassner A, Swabb EA, et al. Lack of cross-reactivity between aztreonam, a monobactam antibiotic and penicillin in penicillin-allergic subjects. J Infect Dis 1984; 149:16–22.
43. Saxon, A Adelman DC, Patel A, et al. Imipenem cross-reactivity with penicillin in humans. J Allergy Clin Immunol 1988; 82:213–217.
44. Beumont MG, Graziani A, Ubel PA, MacGregor RR. Safety of dapsone as Pneumocystis carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with allergy to trimethoprim/sulfamethoxazole. Am J Med 1996; 100:611–616.
45. Holtzer CD, Flaherty JF Jr, Coleman RL. Cross-reactivity in HIV-infected patients switched from trimethoprim-sulfamethoxazole to dapsone. Pharmacotherapy 1998; 18:831–835.
46. Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. J Allergy Clin Immunol 1998; 102(6 Pt 1):1033–1036.
47. Demoly P, Messaad D, Reynes J, et al. Trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients: long-term follow-up regarding efficacy and safety. J Allergy Clin Immunol 2000; 105:588–589.
48. Carr A, Swanson C, Penny R, Cooper DA. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulphamethoxazole in patients with Pneumocystis carinii pneumonia and AIDS. J Infect Dis 1993; 167:180–185.
49. Assouad M, Willcort RJ, Goodman PH. Anaphylactoid reactions to ciprofloxacin [letter]. Ann Intern Med 1995; 122:396–397.
50. Gea-Banacloche JC, Metcalfe DD. Ciprofloxacin desensitization. J Allergy Clin Immunol 1996; 97:1426–1427.
51. Moscicki RA, Sockin SM, Corsello BF, et el. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. J Allergy Clin Immunol 1990; 86:325–332.
52. Abuaf N, Bakoliarisoa R, Ghazouani E, et al. Validation of a flow cytometric assay detecting in vitro basophil activation for the diagnosis of muscle relaxant allergy. J Allergy Clin Immunol 1999; 104:411–418.
53. Porri F, Pradal M, Rud C, et al. Is systemic preoperative screening for muscle relaxant and latex allergy advisable? Allergy 1995; 50:374–377.
54. Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. J Allergy Clin Immunol 1996; 97:933–937.
55. Healy DP, Sahai JV, Fuller SH, Polk RE. Vancomycin-induced histamine release and "red man syndrome": comparison of 1- and 2-hour infusions. Antimicrob Agents Chemother 1990; 34:550–554.
56. Weiss ME, Adkinson NF, Jr. Allergy to protamine. Clin Rev Allergy 1991; 9:339–355.
57. Gottschlich GM, Gravlee GP, Georgitis JW. Adverse reactions to protamine sulfate during cardiac surgery in diabetic and non-diabetic patients. Ann Allergy 1988; 61:277–281.
58. Szczelik A, Stevenson DD. Aspirin induced asthma: advances in pathogenesis and management. J Allergy Clin Immunol 1999; 104:5–13.
59. Stevenson DD. Approach to the patient with a history of adverse reactions to aspirin or NSAIDs: diagnosis and treatment. Allergy Asthma Proc 2000; 21:25–31.
60. Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. J Allergy Clin Immunol 2001; 108:47–51.
61. Stevenson DD, Hankammer MA, Mathison DA, et al. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitus-asthma: long-term outcomes. J Allergy Clin Immunol 1996; 98:751–758.
62. Wong JT, Nagy CS, Krinzman SJ, et al. Repeat oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. J Allergy Clin Immunol 2000; 105:997–1001.
63. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. JAMA 1997; 278:232–233.
64. Stellato C, Adkinson NF, Jr. Pathology of contrast media anaphylactoid reactions: new perspectives on an old problem. Allergy 1998; 53:1111–1113.
65. Steinberg EP, Moore RD, Powe NR, et al. Safety and cost effectiveness of high-osmolality as compared with low-osmolality contrast material in patients undergoing cardiac angiography. N Engl J Med 1992; 326:425–430.
66. Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. J Allergy Clin Immunol 1991; 87:867–872.
67. Lang D, Alpern M, Visintainer P, Smith ST. Increased risk of anaphylactoid reaction from contrast media in patients receiving beta-adrenergic blockers with asthma. Ann Intern Med 1991; 15:270–276.
68. Brockow K, Becker W, Worret WI, Ring J. Late skin test reactions to radiocontrast medium. J Allergy Clin Immunol 1999; 104:1107–1108.
69. Kelso JM. The gelatin story [editorial]. J Allergy Clin Immunol 1999; 103:200–202.
70. Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med 2000; 160:2819–2822.
71. Khoury L, Warrington R. The multiple drug allergy syndrome: a matched-control retrospective study in patients allergic to penicillin. J Allergy Clin Immunol 1996; 98:462–464.

Meconium Enhances the Growth of Perinatal Bacterial Pathogens

Arda Lembet, M.D.[1], Sreedhar Gaddipati, M.D.[2], Ian R. Holzman, M.D.[3],
Richard L. Berkowitz, M.D.[4], and Edward J. Bottone, Ph.D.[5]

Abstract

Objective: To demonstrate the effects of meconium on growth of bacterial pathogens, which are common causes of intra-amniotic infection and neonatal sepsis.

Methods: Meconium collected from 9 healthy neonates was suspended as a 20% solution using sterile saline. In experiment 1, separate test tubes of meconium solution and sterile saline (the control) were individually inoculated with 10^6 colony-forming units of a single species of the following test pathogens: *Escherichia coli, Enterococcus faecalis*, group B *Streptococcus, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Listeria monocytogenes.* After incubation at 37°C for 24 hours, 1 μL each of the bacterial-meconium and bacterial-saline solutions was inoculated onto 5% sheep blood agar. After 24 hours of incubation, the number of developing colonies was counted. In experiment 2, equal volumes of meconium and saline solutions were inoculated with 10^5 colony-forming units of either *E. coli* or group B *Streptococcus*. At intervals of 6, 9, and 24 hours post-incubation, 1 μL each of the bacterial-meconium and bacterial-saline solutions was inoculated onto 5% sheep blood agar plates, and colonies were counted after overnight incubation.

Results: In the first experiment, 24 hours of incubation resulted in bacterial amplification in the meconium solution from an initial inoculum of 10^6 colony-forming units/mL to 10^9 colony-forming units/mL. In contrast, the same inoculation of saline solution (control) showed no increase in colony counts over the same time interval. For *E. coli* and group B *Streptococcus* in experiment 2, growth enhancement in meconium was seen as early as 6 hours, as colony counts of a test species increased from 10^5 colony-forming units/mL to 10^9–10^{10} colony-forming units/mL.

Conclusion: Enhanced growth of perinatal pathogens in meconium was constantly observed, and can occur as early as 6 hours after bacterial interaction of meconium.

Key Words: Meconium, chorioamnionitis, intra-amniotic infection, bacterial pathogens, neonatal sepsis, amnioinfusion, *Escherichia coli*, group B *Streptococcus*.

Background

Meconium has been associated with an increased incidence of intra-amniotic infection because it alters the bacteriostatic properties of amniotic fluid and inhibits host immune defenses. Several investigators working with *Escherichia coli, Listeria monocytogenes, Staphylococcus aureus* and group B *Streptococcus* (GBS) have shown that the addition of meconium to amniotic fluid enhances the growth of these bacterial species (1, 2). In this study, our goal was to utilize a broad range of common obstetric and neonatal pathogens associated with chorioamnionitis and neonatal sepsis to address the following questions: (a) Does meconium enhance bacterial growth under otherwise sterile conditions? And if so, (b) Over what time period does enhanced growth take place?

Methods

Experiments 1 and 2

Fresh meconium was collected within 18 hours of delivery from singleton, term, healthy

---

[1]Fellow, [2]Assistant Professor, and [4]Professor, Division of Maternal Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences; [3]Professor, Department of Pediatrics; and [5]Professor, Division of Infectious Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Initially presented as abstract/poster T559 at the 45th Annual Meeting of the Society for Gynecologic Investigation in Atlanta, Georgia, (Mar 11 – 14. 1998); published as an abstract only in the *Journal of the Society for Gynecologic Investigation*, Vol. 5, #1 (Supplement), Jan/Feb 1998. This manuscript was updated as of March 7, 2002.

Address all correspondence to Sreedhar Gaddipati, M.D., Department of Obstetrics, Gynecology, and Reproductive Sciences, Box 1171, Mount Sinai School of Medicine, 100 East 100th Street, New York, NY 10029; email:sreegaddipati@mssm.edu

infants of women whose pregnancies were uncomplicated. Meconium was taken from a diaper and placed into a sterile container. Immediately after collection, a solution of meconium (weight/volume) was prepared in sterile saline lacking bacteriostatic additives. The meconium was brought into solution by mechanical agitation. This solution visually corresponded to the clinically defined "thick meconium" or "pea soup" appearance. The concentration was such that when a bacterial solution was added to the meconium, the final concentration was 20%. Sterility of the meconium solution was assured by plating 1 mL of this freshly prepared meconium solution onto 5% sheep blood agar (SBA) prior to bacterial addition and observing for growth after 24- hour incubation. This was done concurrently with all trials in both experiments. The bacterial species tested in this study were isolated from clinical specimens (blood, urine) submitted to the microbiology laboratory at The Mount Sinai Hospital. Stock solutions for each bacterial species were prepared by emulsifying several colonies of a given bacterium obtained from a 24-hour culture grown on SBA plates. Bacterial solutions were prepared by addition of the following bacteria to sterile saline without bacteriostatic additives: *E. coli, Enterococcus faecalis,* GBS, *S. aureus, Pseudomonas aeruginosa,* and *L. monocytogenes.* Stock bacterial solutions were made to the concentration of 10^9 colony-forming units per milliliter (10^9 cfu/mL). This was accomplished by visually adjusting the optical density of each stock bacterial solution through use of a McFarland #3 density standard (3) to equal 10^9 cfu/mL. All incubations of SBA plates occurred for 24 hours post-inoculation at 37°C in ambient air; solutions were incubated under the same conditions but at variable times, depending on the specified protocol.

Experiment 1

One μL of a test bacterial solution was individually transferred to 1.0 mL of sterile saline or to 1.0 mL of 20% meconium solution. After gently mixing the contents, 1 μL of each solution was plated onto SBA at time zero (T_0); the test and control mixtures were then incubated for 24 hours, and colonies counted. The remaining meconium and sterile saline solutions were incubated for 24 hours at 37°C in ambient air, after which 1 μL of each solution was plated to SBA at time 24 hours (T_{24}) and incubated for 24 hours; then colonies were counted. This protocol was repeated 5 times with meconium obtained from 5 different neonates. In each trial, stock bacterial solutions were freshly created so as to deliver approximately 10^6 cfu of the test pathogen to the meconium and sterile saline solution. Within each trial, solutions were plated in duplicate.

Experiment 2

This experiment was repeated 4 times in duplicate with meconium obtained from four other neonates. For *E. coli* and GBS, fresh stock solutions were prepared to a concentration of 10^6 cfu/mL. Then, 0.1 mL of a test pathogen was delivered to 0.9 mL sterile saline and similarly to 0.9 mL of 22.2% meconium solution. Immediately thereafter, 1 μL of each solution was plated onto duplicate SBA (T_0), and the plates were incubated. The remaining meconium and saline solutions were incubated. At 6, 9, and 24 hours post-inoculation, 1 μL of each solution was plated onto SBA plates and incubated for 24 hours; the resultant colonies were counted.

Statistics

Due to small sample sizes and not assuming a normal distribution, nonparametric testing was used to analyze the data (Mann-Whitney U test). For experiment 2, logarithmic transformation of the mean values was performed, thus allowing analysis by t test.

Results

Statistical analysis was performed to verify that at T_0, there was no difference in the amount of microorganisms delivered to both saline and meconium solutions in both experiments ($p>0.1$, data not shown). In experiment 1 (Table 1), for each test microorganism, the colony counts at 24 hours post-inoculation in saline solution fell to 10^2 cfu/mL (with the exception of *Pseudomonas*, which remained at 10^6 cfu/mL). Significant enhancement of growth, however, was seen in the meconium solution group at 24-hours post-inoculation ($p<0.05$), which resulted in confluent growth of colonies (i.e., the agar surface was covered by a lawn of colonies). Because individual colonies could not be counted, in order to assess the actual cfu number that resulted in confluent growth, 1 μL from the bacterial-meconium solution was transferred to 1.0 mL of sterile saline, and then 10-fold serial dilutions were performed, plating 0.1 mL onto

TABLE 1

The Growth of Various Pathogens in Saline and Meconium Solution 24 Hours after an Initial Inoculum of ≅10^6 Colony-Forming Units/mL

Pathogen	Saline (Control)	Meconium (Study)
Escherichia coli	10^2	10^9
Enterococcus faecalis	10^2	10^9
Group B *Streptococcus*	10^2	10^9
Staphylococcus aureus	10^2	10^9
Listeria monocytogenes	10^2	10^9
Pseudomonas aeruginosa	10^6	10^9

The numbers show the amount of bacterial pathogens in colony-forming units/mL.
Each experiment was replicated 5 times. The difference between meconium and saline is statistically significant.

TABLE 2

The Growth of Escherichia coli in Saline and Meconium Solution at Varying Time Intervals after an Initial Inoculum of ≅10^5 Colony-Forming Units/mL

Inoculated Solution	6 Hours	9 Hours	24 Hours
Saline 1	0	0	0
Meconium 1	10^9	10^9	2×10^{10}
Saline 2	0	0	0
Meconium 2	3.4×10^9	10^9	10^9
Saline 3	10^5 *	0	0
Meconium 3	10^9	10^9	10^9
Saline 4	0	0	0
Meconium 4	10^9	10^9	10^9

* see text

TABLE 3

The Growth of Group B Streptococcus in Saline and Meconium Solution at Varying Time Intervals after an Initial Inoculum of ≅10^5 Colony-Forming Units/mL

Infected Solution	6 Hours*	9 Hours*	24 Hours*
Saline 1	10^5	10^7	0
Meconium 1	10^9	10^9	10^9
Saline 2	0	0	0
Meconium 2	3.4×10^9	10^9	10^9
Saline 3	0	0	0
Meconium 3	10^9	10^9	10^9
Saline 4	0	0	0
Meconium 4	10^9	10^9	10^9

The numbers show the amount of group B *Streptococcus* in colony-forming units/mL.
* = statistically significant numbers

SBA at each dilution. Through this method it was determined that confluent growth of bacteria occurred when the count was 10^9–10^{10} cfu/mL. This was performed with only one of the trials, and for statistical analysis, confluence was assumed to be 10^9 cfu/mL in all five trials.

To further quantitate the role of meconium enhancement of bacterial growth, colony counts of *E. coli* and GBS were assessed by sampling the bacterial-saline and bacterial-meconium mixtures at different time intervals (experiment 2, Tables 2 and 3). Subculture of saline inoculated with *E. coli* demonstrated no growth after 6 hours (3 of 4 trials, Table 2). In the one contrary instance, 10^5 cfu/mL of *E. coli* were present at 6, but at 9 and 24 hours *E. coli* were absent. This may have been due to a sampling error. In contrast, co-cultivation of *E. coli* in meconium resulted in growth increase from 10^5 cfu/mL to 10^9 cfu/mL at 6, 9, and 24 hours ($p=0.01$). Similar results were recorded for GBS (Table 3). GBS persisted in the saline control in trial 1 until 9 hours post-inoculation; for trials 2–4, GBS was absent by 6 hours post-inoculation. Meconium inoculated with GBS, however, demonstrated significant growth as early as 6 hours ($p=0.009$).

Conclusions

Despite the antibacterial properties of amniotic fluid, when intra-amniotic infection occurs, it poses a significant risk both for the mother and the neonate. The inhibitory effect of amniotic fluid on bacterial growth may be explained by the presence of trace elements, lysozyme and immunoglobulins, and by the balance between the zinc and phosphate content of the amniotic fluid (4–6). Changes in the ideal composition of the amniotic fluid can lead to its loss of antibacterial properties, and can even promote bacterial growth. Meconium-contaminated amniotic fluid is suspected to be an important factor which can lead to such alteration.

Meconium-related enhancement of bacterial infection was first demonstrated in a mouse model (1). Meconium injected with *E. coli* intraperitoneally, in comparison to bacterial-saline or bacterial-amniotic fluid injections, effected a reduction in LD50 (organisms/mouse) by a factor of 7.5–6800. The mechanism causing meconium enhancement of bacterial growth is unclear. In recent years, an increase in intra-amniotic infection in patients with meconium-stained amniotic fluid has been documented in clinical studies (7, 8).

In this *in vitro* study, we demonstrated growth-enhancing effect of meconium for different neonatal pathogens. A similar experimental design by Florman and Teubner (2) demonstrated that meconium at a concentration of 1% enhanced growth for *E. coli*, *S. aureus* and *L. monocytogenes* (2). Our study (a) confirmed their results for those three species but also expanded the spectrum of species tested, and (b) demonstrated that growth enhancement occurred at a higher meconium concentration (20% versus 1%). In experiment 1, all five trials demonstrated that meconium enhanced bacterial growth in comparison to saline-inoculated solution (controls). Experiment 2 clearly showed that bacterial growth enhancement in meconium occurred as early as 6 hours after cocultivation. In this setting, bacterial colony counts for the tested species increased from an initial 10^5 cfu/mL to 10^9–10^{10} cfu/mL at 6, 9, and 24 hours.

Several related issues were not addressed in this study. The study by Florman and Teubner (2) used amniotic fluid rather than saline as the "solvent" to suspend meconium. Amniotic fluid may vary from infant to infant; our goal was to test the effect of meconium alone on bacterial growth enhancement rather than meconium combined with amniotic fluid. However, the design in our study may more closely reflect the clinical setting where there is rupture of membranes and thick meconium present, or where a transcervical amnioinfusion is administered to reduce the thickness of the meconium.

With respect to clinical practice, one should be aware of the enhancement of growth of various microorganisms in the presence of meconium. Further research is needed to determine whether antibiotics and/or amnioinfusion are useful strategies to decrease infectious morbidity associated with thick meconium.

References

1. Bryan SC. Enhancement of bacterial infection by meconium. Johns Hopkins Med J 1967; 121:9–13.
2. Florman AL, Teubner D. Enhancement of bacterial growth in amniotic fluid by meconium. J Pediatr 1969; 74:111–114.
3. Hendrickson DA, Krenz MM. Reagents and stains. In: Balows A, editor. Manual of clinical microbiology. 5th ed. Washington (DC): American Society for Microbiology; 1991. p. 1296.
4. Thadepalli H, Bach VT, Davidson EC, Jr. Antimicrobial effect of amniotic fluid. Obstet Gynecol 1978; 52:198–204.
5. Abbasi IA, Hemming VG, Eglinton GS, Johnson TR. Proliferation of group B streptococci in human amniotic fluid in vitro. Am J Obstet Gynecol 1987; 156:95–99.
6. Hoskins IA, Hemming VG, Johnson TR, Winkel CA. Effect of alterations of zinc-to-phosphorus ratios and meconium content on group B Streptococcus growth in human amniotic fluid in vitro. Am J Obstet Gynecol 1987; 157:770–773.
7. Romero R, Hanaoka S, Mazor M, et al. Meconium-stained amniotic fluid. A risk factor for microbial invasion of the amniotic cavity. Am J Obstet Gynecol 1991; 164:859–862.
8. Wen TS, Eriksen NL, Blanco JD, et al. Association of clinical intra-amniotic infection and meconium. Am J Perinat 1993; 10:438–440.

Small Bowel Perforation Secondary to Metastatic Lung Cancer:

A Case Report and Review of the Literature

George H. Sakorafas, M.D.[1], George Pavlakis, M.D.[2], and Kyriakos D. Grigoriadis, M.D.[3]

Abstract

Small bowel perforation is a rare complication of metastatic lung cancer. We were able to document 35 such cases in the literature in English. Aggressive investigation and early surgery is the only method for providing palliation to these patients. However, morbidity and mortality remain high and the prognosis is dire.

Key Words: Abdominal complications, acute abdomen, lung cancer, metastasis, small bowel perforation.

Introduction

LUNG CANCER is the most common cause of cancer-related death in both men and women in Western countries. Approximately 25% of all cancer deaths are attributable to lung cancer (1, 2). Moreover, about one-half of patients with lung cancer have metastatic disease at the time of initial diagnosis, most frequently of the bone, liver, and adrenal glands (2, 3). We report a case of small bowel perforation secondary to metastatic disease of lung cancer, a very rare complication in the natural history of this cancer.

Case Report

A 36-year-old woman presented with a two-month history of cough, fever, fatigue, and weigh loss. During her evaluation, chest radiography showed a lesion at the hilum of the right lung, which had gradually enlarged. Bronchoscopy and biopsy established the diagnosis of a malignant (non-differentiated) tumor. Chest computerized tomography (CT) demonstrated marked mediastinal lymphadenopathy. Diagnostic evaluation for staging of the neoplasm was negative for extrathoracic disease/dissemination. A right pneumonectomy was performed. Postoperative course was uneventful. Histology revealed a high-grade carcinosarcoma in the hilum of the right lung with lymph node metastases. The patient received six cycles of adjuvant chemotherapy with cisplatinum-epirubicin-cyclophosphamide.

Five months later, the patient presented again with severe abdominal pain, diffuse abdominal guarding and rebound tenderness. Laboratory evaluation was without pathological findings, except a marked leukocytosis (WBC = 24,000/mm^3). Abdominal X-ray demonstrated free intraperitoneal air; the patient was operated on with the diagnosis of a perforation of a hollow viscus. At surgery, two masses were found at the surface of two loops of the ileum within the fat of its mesentery. One of these ileal tumors was perforated. The abdominal exploration was without other pathological findings. Two segmental enterectomies with end-to-end anastomosis were performed. Histology showed a poorly differentiated metastatic neoplasm involving the ileum, consistent with the primary lung tumor (Figure). Postoperative course was uneventful and the patient discharged on postoperative day 7.

Four weeks later the patient presented again with weakness of the right arm. Neurological examination and CT scan showed the presence of brain metastases and enlarged mediastinal

---

From the Departments of [1]Surgery, [2]Medical Oncology and [3]Pathology, 251 Hellenic Air Force Hospital, Athens, Greece.

Address all correspondence to G.H. Sakorafas, M.D., Arkadias 19-21, GR-115 26 Athens, Greece; E-mail: georgesakorafas@yahoo.com

This manuscript was updated as of March 7, 2002.

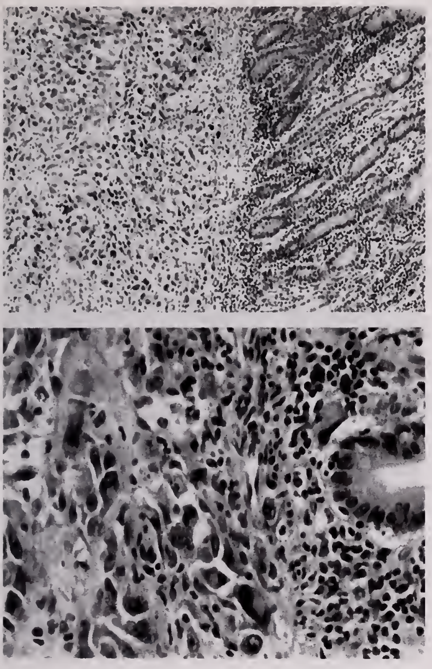

Fig. (Upper panel) Metastasis of carcinoma at the intestine's submucosal area under the normal glands (H & E × 150). **(Lower panel)** Higher magnification of metastatic tumor cells (H & E × 400).

lymph nodes. The patient died 4 weeks later, two months after abdominal surgery, from generalized disease.

Discussion

Despite the early and widespread dissemination of lung carcinoma to many body sites, clinically significant metastases isolated in the small bowel are rare and typically occur only in the advanced stages of the disease. The extent of metastatic disease in the natural history of lung cancer correlates with its histologic type (greatest for large and small cell carcinoma, least for squamous cell carcinoma). Isolated reports of small bowel perforation caused by metastatic lesions of various origins appeared in the literature during the first half of the 20th century; however, it was not until 1961 that the first case of small bowel perforation secondary to lung cancer was reported by Morgan, Sigel and Wolcott (4). Perforation of the small intestine as a result of these lesions is rare (5–17). Using a Medline search, we were able to document 35 such cases in the world literature in English. The Table lists some of these reported cases in which pulmonary histology was available.

Metastases to the small bowel may present as perforation, obstruction, malabsorption, and/or hemorrhage. Tumor cells metastasizing from lung cancer to the bowel wall by hematogenous routes form a tumor mass (5, 6), which replaces all or part of the bowel wall and results in various symptoms. If tumor necrosis should occur for any reason (e.g., after intense chemotherapy, as is seen with leukemia and lymphoma) (5, 18), perforation may ensue. If the mural tumor remains viable and grows into the bowel lumen, obstruction, instead of perforation, will occur. Furthermore, ulceration or

TABLE

Small Bowel Perforation Secondary to Metastatic Lung Cancer Review of the Literature in English

Reference Number	Year	Number of Patients	Histology
17	1967	1	Adenocarcinoma
16	1969	1	Large cell carcinoma
5	1981	1	Epidermoid carcinoma
13	1979	1	Adenocarcinoma
14	1977	1	Adenocarcinoma
15	1976	1	Squamous cell carcinoma
12	1982	3	Squamous cell carcinoma
12	1982	2	Undifferentiated carcinoma
12	1982	1	Adenosquamous carcinoma
11	1985	1	Squamous cell carcinoma
9	1992	1	Squamous cell carcinoma
9	1992	2	Adenocarcinoma
10	2001	1	Adenocarcinoma

Flow Cytometry

Flow cytometry was performed on lysed peripheral blood and bone marrow aspirate using the Beckman-Coulter EPICS XL/MCL flow cytometer (Beckman-Coulter, Fullerton, CA) and dual-color staining. Antibodies utilized were: CD5, CD10, CD19, CD20, CD22, CD23, CD45, kappa and lambda (Beckman-Coulter, Fullerton, CA).

Results

Case 1

An 82-year-old man presented with a 4-month history of fevers, night sweats, and hypotension. The history was remarkable for monoclonal gammopathy of undetermined significance. Physical examination revealed hepatosplenomegaly but no lymphadenopathy. Laboratory studies revealed hemoglobin 119 g/L, hematocrit 34.8%, platelets 53 × 10^9/L, white blood cells 10.1 × 10^9/L with 34% segmented neutrophils, 17% lymphocytes, 2% atypical lymphocytes, 14% monocytes, 2% eosinophils, 2% basophils, 14% band neutrophils, 4% neutrophilic metamyelocytes, 7% neutrophilic myelocytes, 3% blasts, 1% plasma cells, and 1 nucleated red blood cell per 100 white blood cells. LDH was 695 U/L (normal < 220). Serum immunoglobulins were IgG 18.8 g/L, IgA 1.45 g/L, and IgM 13.5 g/L. IgG kappa and IgM kappa monoclonal proteins were identified on immunofixation and accounted for 40% of the IgG and 70% of the IgM.

Bone marrow biopsy and aspiration were performed. The bone marrow biopsy specimen was hypercellular (80%), diffusely infiltrated by blasts with round-to-ovoid nuclei, one or two inconspicuous nucleoli, and scant cytoplasm (Fig. 1). Leder stain (chloroacetate esterase) was positive in residual granulocytic precursors but negative in the blast cells. The bone marrow aspirate smears showed sheets of blasts with round-to-ovoid nuclei, finely distributed chromatin, one or two nucleoli, a rim of agranular, faintly basophilic cytoplasm, and numerous "lymphoglandular bodies" scattered between the blasts (Fig. 2). Flow cytometry on bone marrow aspirate demonstrated a monoclonal B-cell phenotype (CD5-, CD10+, CD19+, CD20+, CD22+, CD23-, CD45+, surface immunoglobulin lambda light chain). A diagnosis of DLBCL was established. Chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) was administered and the patient showed improvement.

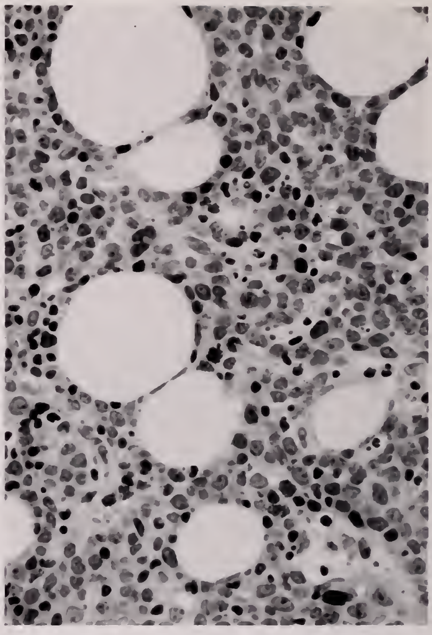

Fig. 1. Bone marrow biopsy specimen from Case 1, showing diffuse infiltration by blasts. A "leukemic" pattern is present with preservation of fat cells and scattered eosinophilic myelocytes (Hematoxylin & Eosin, × 200).

Case 2

An 86-year-old man presented with back pain, fever, and leg weakness. The medical history revealed prostatic adenocarcinoma, Gleason's pattern 4+4, score = 8, diagnosed 4 years previously and treated with hormonal therapy. Physical examination revealed no lymphadenopathy. There was bilateral lower-motor-neuron weakness of the lower extremities. Laboratory studies revealed hemoglobin 91 g/L, hematocrit 25.9%, platelets 98 × 10^9/L, white blood cells 7.3 × 10^9/L with 47% segmented neutrophils, 7% lymphocytes, 5% atypical lymphocytes, 5% monocytes, 19% band neutrophils, 5% neutrophilic metamyelocytes, 11% neutrophilic myelocytes, 1% promyelocytes, and 6 nucleated red blood cells per 100 white

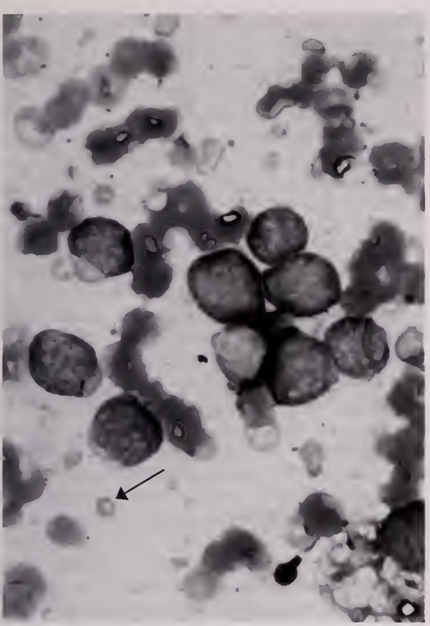

Fig. 2. Bone marrow aspirate smear from Case 1, showing blasts with faintly basophilic agranular cytoplasm. "Lymphoglandular bodies," pale basophilic globules (arrow) of varying size, are present between the cells (Giemsa, × 600).

blood cells. Serum prostate-specific antigen (PSA) was 0.1 ng/mL. CT scan of the abdomen and pelvis showed minimally enlarged para-aortic and presacral lymph nodes. Bone scan was negative. A tentative diagnosis of metastatic prostatic adenocarcinoma with cauda equina syndrome was made and radiotherapy was begun.

Bone marrow biopsy and aspiration were performed. The bone marrow biopsy specimen was hypercellular (80%) with extensive coagulative necrosis. Foci of viable marrow were diffusely replaced by blasts with round-to-ovoid nuclei, one or two inconspicuous nucleoli, and scant cytoplasm. Leder stain (chloroacetate esterase) was negative. The bone marrow aspirate smear showed sheets of cells with pyknotic degenerating nuclei admixed with scattered viable blasts with round-to-ovoid nuclei, one or two nucleoli, and moderately abundant, deeply basophilic cytoplasm with occasional cytoplasmic vacuoles. Flow cytometry on peripheral blood demonstrated a monoclonal B-cell phenotype (CD5-, CD10+, CD19+, CD20+, CD22+, CD23-, CD45+, surface immunoglobulin lambda light chain). A diagnosis of DLBCL was established. Chemotherapy with cyclophosphamide, vincristine, and methotrexate was administered, but the patient expired due to sepsis and neutropenia 10 days later. Autopsy was not performed.

Case 3

A 76-year-old woman presented with syncope and a 2-month history of malaise and weight loss. Laboratory studies revealed hemoglobin 95 g/L, hematocrit 28.0%, platelets 34 × 10^9/L, white blood cells 5.4 × 10^9/L with 41% segmented neutrophils, 26% lymphocytes, 11% monocytes, 1% basophils, 17% band neutrophils, 2% neutrophilic metamyelocytes, and 2% neutrophilic myelocytes. Rare nucleated red blood cells (< 1 per 100 white blood cells) were present. Serum calcium was 3.82 mmol/L (normal 2.20–2.60 mmol/L). LDH was 434 U/L (normal < 220) and alkaline phosphatase 213 U/L (normal < 110). Physical examination was unremarkable. There was no lymphadenopathy. Gallium scan revealed an ill-defined area of uptake in the pulmonary hila and posterior mediastinum. CT scan of the chest and abdomen was negative, except for multiple rib fractures.

Bone marrow biopsy and aspiration were performed. Bone marrow could not be aspirated. The bone marrow biopsy was markedly hypercellular (100%), with extensive coagulative necrosis. Areas of viable marrow were replaced by sheets of blasts with irregular, ovoid-to-lobated nuclei, inconspicuous nucleoli and scant cytoplasm. Immunohistochemical staining demonstrated a B-cell phenotype (CD5-, CD10-, CD20+, CD45+, kappa and lambda immunoglobulin light chain negative). A diagnosis of DLBCL was established. The patient was treated with vigorous hydration and forced diuresis with resolution of the hypercalcemia. Chemotherapy with CHOP was administered and the patient showed improvement.

Case 4

A 45-year-old woman presented to her physician with generalized weakness. Physical examination was unrevealing. There was no lymphadenopathy. Laboratory studies revealed hemoglobin 67 g/L, hematocrit 19.4%, platelets

88 × 10^9/L, white blood cells 3.3 × 10^9/L with 32% segmented neutrophils, 56% lymphocytes, and 12% monocytes.

Bone marrow biopsy and aspiration were performed. Bone marrow could not be aspirated. The bone marrow biopsy was hypercellular with reticulin fibrosis, increased immature forms of uncertain lineage, and atypical megakaryocytes. A diagnosis of a myelodysplastic syndrome was entertained. A bone marrow biopsy was repeated six months later. The bone marrow biopsy was markedly hypercellular (100%), with a diffuse infiltrate of large blasts with ovoid-to-lobated nuclei, prominent nucleoli and abundant pale cytoplasm, admixed with small, atypical lymphocytes with irregular, twisted nuclei. Immunohistochemical staining demonstrated a B-cell phenotype (CD5-, CD10-, CD20+, CD45+, kappa and lambda immunoglobulin light chain negative). A diagnosis of DLBCL was established. Chemotherapy with CHOP was administered. There was a complete response, which was followed by bone marrow relapse 14 months later. She subsequently received a bone marrow transplant and is free of disease four years later.

Discussion

Bone marrow involvement is less frequent at presentation in diffuse large B-cell lymphoma than it is in low-grade B-cell lymphomas (chronic lymphocytic leukemia / small lymphocytic lymphoma, follicle center lymphoma, and mantle cell lymphoma) (1–3). However, T-cell-rich DLBCL, characterized by a major component of reactive T cells, is an apparent exception, with marrow involvement in up to 62% of cases (4). In the present series, we report on four cases of diffuse large cell lymphoma which presented primarily as bone marrow disease with hematologic manifestations, including leukoerythroblastosis and pancytopenia (Table 1). Lymphadenopathy in these cases was absent or inconspicuous. In each case, the prominence of hematologic manifestations led to consideration of alternative diagnoses, including acute granulocytic leukemia and a myelodysplastic syndrome. The presence of circulating immature granulocytes and diffuse marrow replacement by blasts suggested acute granulocytic leukemia in three patients; in the fourth, the presence of pancytopenia and scattered single blasts in the bone marrow suggested a myelodysplastic syndrome. A clue to the correct diagnosis, in the one case in which they were prominent, Case 1, was the presence of numerous "lymphoglandular bodies" in the bone marrow aspirate smear (Fig. 2). These extracellular basophilic bodies, globules of extruded cytoplasm, are well known to cytopathologists to be a feature of malignant lymphoma in fine-needle aspiration smears, but are less familiar to surgical pathologists and hematologists. The presence of "lymphoglandular bodies" in bone marrow aspiration smears has been reported to be a clue to the presence of B-cell malignancy (10).

In three of these cases, additional clinical manifestations associated with lymphoma were present: monoclonal gammopathy in Case 1, sepsis and neutropenia in Case 2, and life-threatening hypercalcemia in Case 3. Monoclonal gammopathy of undetermined significance (defined by a monoclonal serum protein of less than 30 g/L and the absence of anemia, hypercalcemia, lytic bone lesions, or bone marrow plasmacytosis exceeding 10%) is associated with progression to multiple myeloma, lymphoma, amyloidosis, chronic lymphocytic leukemia, or Waldenström's macroglobulinemia in up to 30% of patients with long-term follow-up, at a rate of approximately 1% per year (11). Although this patient (Case 1) had an IgM paraprotein, he did not meet the criteria for Waldenström's macroglobulinemia, since his serum IgM paraprotein was less than 30 g/L. Sepsis and neutropenia are recognized complications

TABLE 1
Hematologic Findings

Case	Hgb g/L	Hct %	WBC ×10^9/L	PLT	PMN %	LYM %	MON %	BND %	META %	MYE %	BLAST %	NRBC /100 WBC
1	119	34.8	10.1	53	34	19*	14	14	4	7	3	1
2	91	25.9	7.3	98	47	12*	5	19	5	11	1	6
3	95	28.0	5.4	34	41	26	11	17	2	2		rare
4	67	19.4	3.3	88	32	56	12					

*atypical lymphocytes (2% in Case 1; 5% in Case 2).

TABLE 2
Immunophenotypic Studies

Case	CD45	CD5	CD10	CD19	CD20	CD22	CD23	Sig
1 BM*	+	-	+	+	+	+	-	Lambda
2 PB*	+	-	+	+	+	+	-	Lambda
3 BM**	+	-	-	ND	+	ND	ND	-
4 BM**	+	-	-	ND	+	ND	ND	-

* flow cytometry
**immunohistochemistry
ND = not determined

of cytotoxic chemotherapy for malignant lymphoma and other neoplasms. The extensive marrow replacement by lymphoma in these patients may predispose to neutropenia as a result of limited bone marrow reserve; in one patient (Case 4), mild neutropenia was present at presentation. Life-threatening hypercalcemia is an infrequent complication of malignant lymphoma, which is humorally mediated in most cases (12). Hydration and diuresis are the mainstays of therapy; addition of biphosphonates, calcitonin, mithramycin, or gallium nitrate may be necessary in refractory cases. Bone marrow necrosis was a prominent feature in the biopsies in Case 2 and Case 3. Bone marrow necrosis may be the presenting feature of hematologic malignancies, including acute leukemia (13, 14) and malignant lymphoma (7). The diagnosis of malignant lymphoma in these cases was ultimately established by immunophenotypic studies (Table 2) utilizing immunofluorescence flow cytometry (Cases 1 and 2) or immunohistochemical staining of bone marrow sections (Cases 3 and 4).

The origin of the bone marrow lymphoma in these patients is unclear. Although some evidence of extramedullary involvement was present in three cases (hepatosplenomegaly in Case 1, retroperitoneal lymphadenopathy in Case 2, positive gallium scan in Case 3), extramedullary involvement in these cases was clinically inconspicuous, suggesting the possibility of primary bone marrow lymphoma. Cases of primary bone marrow lymphoma are reported in the literature (5–9); however, the criteria for diagnosis are not well established. It is hypothesized that primary bone marrow lymphoma could arise from lymphoid follicles normally present in the bone marrow, which increase with age (15). Since the criteria for primary bone marrow lymphoma are not well established, these cases could be considered as diffuse large B-cell lymphoma presenting as bone marrow involvement, rather than as primary bone marrow lymphoma *per se*; however, this distinction seems semantic and a bone marrow origin of these lymphomas seems likely on clinical and pathologic grounds.

Diffuse large B-cell lymphoma may present with bone marrow involvement mimicking a primary hematologic disorder as the major manifestation. Immunophenotypic studies are necessary for diagnosis. DLBCL should be considered in the differential diagnosis of unusual hematologic presentations, particularly in the elderly.

References

1. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982; 49:2112–2135.
2. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphomas. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997; 89:3909–3918.
3. Pittaluga S, Bijnens L, Teodorovic I, et al. Clinical analysis of 670 cases in two trials of the European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group subtyped according to the Revised European-American Classification of Lymphoid Neoplasms: a comparison with the Working Formulation. Blood 1996; 87:4358–4367.
4. Skinnider BF, Connors JM, Gascoyne RD. Bone marrow involvement in T-cell-rich B-cell lymphoma. Am J Clin Pathol 1997; 108:570–578.
5. Staples WG, Getaz EP. Bone marrow involvement in malignant lymphoma without peripheral lymphadenopathy. S Afr Med J 1977; 52:60–63.
6. Ponzoni M, Li CY. Isolated bone marrow non-Hodgkin's lymphomas: a clinicopathologic study. Mayo Clin Proc 1994; 69:37–43.
7. Majumdar G. Massive bone marrow necrosis as the presenting feature in a case of primary bone marrow high grade non-Hodgkin's lymphoma. Leukemia Lymphoma 1997; 26:409–412.
8. Wong KF, Chan JK, Ng CS, et al. Large cell lymphoma with initial presentation in the bone marrow. Hematol Oncol 1992; 10:261–271.

9. Barton JC, Conrad ME, Vogler LB, Parmley RT. Isolated marrow lymphoma: an entity of possible T-cell derivation. Cancer 1980; 46:1767–1774.
10. Stern RC, Liu K, Dodge RK, et al. Significance of lymphoglandular bodies in bone marrow aspiration smears. Diagn Cytopathol 2001; 24:240–243.
11. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002; 346:564–569.
12. Daroszewska A, Bucknall RC, Chu P, Fraser WD. Severe hypercalcemia in B-cell lymphoma: combined effects of PTH-rP, IL-6, and TNF. Postgrad Med J 1999; 75:672–674.
13. Navari RM, Carter J, Hillmon RS. Bone marrow necrosis in acute leukemia. Acta Haematologica 1983; 69:158–163.
14. Niebrugge DJ, Benjamin DR. Bone marrow necrosis preceding acute lymphoblastic leukemia in childhood. Cancer 1983; 52:2162–2164.
15. Rywlin AM, Ortega RS, Dominguez CJ. Lymphoid nodules of bone marrow: normal and abnormal. Blood 1974; 43:389–400.

INFORMATION FOR AUTHORS

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of The Mount Sinai Hospital*, is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and other major databases. The abstract and full text of each published article is posted on *The Journal's* web site <www.mssm.edu/msjournal> where it can be accessed by the reader. *The Journal's* web site is linked to that of the National Library of Medicine. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcomed. *The Journal* generally follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as revised in 1997and modified by *The Journal* to conform to the style employed by it.. *The Journal* aims at responding to authors of manuscripts within 8 weeks of submission.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@mssm.edu; world wide web: www.mssm.edu/msjournal.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and either (3) the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in *The Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal*'s office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations and a disk (see below). **Manuscripts must be computer generated, double spaced throughout (including references, legends, and tables)**, on one side of $8^1/2$ x 11 inch white bond paper with **one inch** margins. The title page must be entirely separate and should designate the location(s) where the work was done, and the name and address of the corresponding author. The abstract page(s) should be numbered sequentially as i, ii, iii, etc. A separate page should be used for each table. The legends, in numerical sequence, should be typed together on one or more pages (if needed). A separate page, or pages, should list the references in the sequential order they are cited for the first time in the narrative text. A disk should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted (Windows, MAC), and the software used (WordPerfect, MS Word, etc.). PC format is preferred, but a high-density, formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or WordPerfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page(s) or in legends. Define all abbreviations on first use in the body of the manuscript. All abbreviations used in a table must be defined at the bottom of the table.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher, giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office (or its equivalent) which supervises such work.

Title Page. This page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, and middle initial(s), if any, and not more than two academic degrees; (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and telephone and FAX numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom an offprint is to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and (9) **a running head of fewer than 40 letter spaces.** At the bottom of the title page, **list 3 to 10 key words or phrases** to facilitate computer searches in accord with medical subject headings from *Index Medicus.* If more than one sheet is needed, label the supplemental sheet as "Title Page (cont.)."

Abstract. All articles must include an abstract of not more than 400 words. The pages containing the abstract should be numbered sequentially as i, ii, iii, etc. This abstract will be published in *The Journal* with the article. Enough detail should be provided in the abstract so that it will be sufficiently informative to stand alone when placed on *The Journal*'s web page prior to publication of the entire article in *The Journal.* Abstracts should be double spaced. Abstracts for manuscripts specifically describing original clinical and/or laboratory research should be structured in four paragraphs:

> **Background:** what problem(s) was (were) addressed;
> **Methods:** how the study was performed;
> **Results:** the most significant results;
> **Conclusions.**

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page and also after the abstract to facilitate computer searches. **Repeat at the end of the abstract the same key words which are listed on the title page.**

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning, in conformity with the style used by *The Journal.* Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of $3^{1}/_{8}$ inches. **The type of stain and power of magnification (e.g., 10x, 40x, 100x, etc.) must be indicated in the relevant legend**. Electron photomicrographs should have internal scale markers. On the back of each print and photograph, affix a gum label on which the number of the figure has been written to correspond to its identification in the text, as well as the title of the manuscript, first author's last name, and the word "top" and an arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial features should be masked to prevent identification of the subject unless they include details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

The Journal does not publish color images unless the author is willing to pay for the additional expense involved. Should the author wish to consider publishing images in color, 3 copies of each color print must be included with the manuscript. If the manuscript is accepted, the author will be informed of the extra cost involved. A check for this amount must be received prior to publication. If, however, the author wishes to have color images appear **only in *The Journal's* web page version** of the article, one copy of each color print (rather than 3) along with the 3 black and white glossy prints must be submitted with the manuscript. The web page version of the manuscript will not involve additional expense to the author.

Legends. Legends should not duplicate the text. They should appear together in numerical order, typed double spaced on one or more pages following the text. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle," etc.) or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Footnotes. Except as noted above in the section "Units of Measurement," the use of footnotes is to be avoided. All relevant information should be incorporated directly into the narrative text and appropriately cited, as noted below in the section "References."

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (**TABLE 1**, etc., in bold type) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text, and type the title, *in italics*, on a separate line below the table's number. Identify all abbreviations and/or symbols used in the table in a footnote at the bottom of the table.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., **Cytomegalovirus (1), steroids (2, 3), and recreational drugs (4–6) have all been implicated (7).** Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus*. The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled "References" are illustrated in the version of "Uniform Requirements" published in *The New England Journal of Medicine* referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style shown in the examples below. The list of references should not be formatted as "Endnotes."

1. Brown LK. Sleep apnea syndromes: Overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309–315.

3. Couser WG. Glomerular diseases. In: Stein J, editor. Internal medicine. 2nd ed. Boston: Little Brown; 1987. pp. 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then "et al."

References to unpublished data (unless the information is in press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission.

If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.

Proofs. A revised, copy-edited manuscript will be sent to the corresponding author as soon as it is available, for necessary corrections only. **Stylistic changes should not be made**. All corrections should be made on this copy, which must be returned to *The Journal* office as soon as possible (see "Communications" above). This corrected, revised, edited version of the manuscript will be sent to the printer for typesetting directly from a disk. "Galleys" will not be sent to the corresponding author for review.

Offprint Orders. A "Request for Offprints" form will be sent to the corresponding author. If offprints are desired, the form must be returned to the editorial office. When the article is scheduled for publication, an "Offprint Order Form" and "Shipping Label" will be sent to the corresponding author. These must be completed and returned with a check for the exact amount in US dollars made out to *The Mount Sinai Journal of Medicine*. Please indicate on the check the last name of the first author, and the title of the article. If, for one reason or another, an "Offprint Order Form" and "Shipping Label" are not received by the corresponding author, they may be obtained directly from *The Journal* office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the total number of printed pages and whether covers are desired. The cost of delivery must be added to the cost of the offprints. Information on the cost of other than routine delivery can be obtained from *The Journal* office.

09/2002

Required Form for Authors

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

Author(s) Signature	Date	Author(s) Signature	Date
1st ______		4th ______	
2nd ______		5th ______	
3rd ______		6th ______	

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal.*

Author(s) Signature	Date	Author(s) Signature	Date
1st ______		4th ______	
2nd ______		5th ______	
3rd ______		6th ______	

4. US Federal Employees

I was an employee of the US government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

Author(s) Signature	Date	Author(s) Signature	Date
1st ______		4th ______	
2nd ______		5th ______	
3rd ______		6th ______	

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

09/2002

THE
MOUNT SINAI JOURN
OF MEDICINE

3 4805 077814 0
LEVY LIBRARY, MT. SINAI SCHOOL OF MEDICINE

Forthcoming: Grand Rounds

Severe Asthma: Epidemiology, Pathophysiology and Treatment
Sally Wenzel
National Jewish Medical and Research Center
Denver, CO

Cardiovascular Disease in Women
W. Lane Duvall
Mount Sinai School of Medicine

Congestive Heart Failure: Guidelines for the Primary Care Physician
Ira Galin and David A. Baran
Mount Sinai School of Medicine

Gender Differences in Pulmonary Disease
Cynthia F. Caracta
Mount Sinai School of Medicine

Immunologic Factors in Transplant Arteriopathy: Insight from Animal Models
Jeffrey D. Alexis, Robert T. Pyo, and Igor Chereshnev
Mount Sinai School of Medicine

Theme Issues

Ethics 1999 — Ethical Limits of Transplantation
Rosamond Rhodes and Daniel A. Moros, Editors

Ethics 2001 — Medicine, Money and Morals
Rosamond Rhodes and Daniel A. Moros, Editors

Minimally Invasive Vascular Surgery: The Evolution of Endovascular Therapy
Michael L. Marin, Larry H. Hollier, Valentin Fuster, Editors

Available now:

Methadone Symposium – Part 1:2000
Volume 67: Numbers 5 & 6. 125 pages, $40.00
Methadone Symposium – Part 2:2001
Volume 68: Number 1. 78 pages, $25.00

Gastroenterology and Hepatology at The Mount Sinai Hospital 1852–2000
Volume 67: Number 1. Part 1:2000 94 pages $20.0
Volume 67: Number 3. Part 2:2000 89 pages $20.0
Volume 68: Number 2. Part 3:2001 80 pages $25.0

Visit our web page — http://www.mssm.edu/msjournal

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 70 NUMBER 3 MAY 2003

THEME ISSUE—ETHICS

Daniel A. Moros, Rosamond Rhodes and Lewis Burrows, guest editors

CONTENTS

Ethical Limits of Transplantation

Introduction *Daniel A. Moros, Rosamond Rhodes and Lewis Burrows*......139

Extension of Organ Transplantation: Some Ethical Considerations *George J. Agich*......141

Hand Transplantation: Current Status *Michael R. Hausman, John Masters, and Albert Panozzo*......148

Uterus Transplantation *Albert Altchek*......154

Laryngeal and Tracheal Transplantation: Ethical Limitations *Eric M. Genden and Mark L. Urken*......163

Stem Cell Transplantation *Steven Fruchtman*......166

Candidate Selection Criteria for Living Donor Liver Transplantation *Myron Schwartz*......171

Trust and Trustworthiness in Organ Transplantation: Good Samaritan and Emotionally Related Living Donors *Rosamond Rhodes*......174

Panel Discussion......178

GRAND ROUNDS

Severe Asthma: Epidemiology, Pathophysiology and Treatment *Sally Wenzel*......185

Immunologic Factors in Transplant Arteriopathy: Insight from Animal Models *Jeffrey D. Alexis, Robert T. Pyo, and Igor Chereshnev*......191

Laboratory Aspects of Tick-Borne Diseases: Lyme, Human Granulocytic Ehrlichiosis and Babesiosis *Maria E. Aguero-Rosenfeld*......197

GENERAL ARTICLES

Lyme Disease Trends — Dutchess County, New York, 1992–2000 *Catherine C. Chow, Andrew S. Evans, Jr., Candace M. Noonan-Toly, Dennis White, Geraldine S. Johnson, Spencer J. Marks, Michael C. Caldwell, and Edward B. Hayes*......207

Information for Authors......i

SAINT BARNABAS
HEALTH CARE SYSTEM

LIBERTY HEALTHCARE SYSTEM, INC.

Veterans
Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by the Mount Sinai Medical Center of New York and has the following affiliates: Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY; Saint Barnabas Health Care System, Livingston, NJ; Newark Beth Israel Medical Center, Newark, NJ; Liberty HealthCare System, Inc., Jersey City, NJ.

Editor-in-Chief

Sherman Kupfer, M.D.

Associate Editors

Harriet S. Gilbert, M.D.
Leslie A. Kuhn, M.D.
Philip S. Ledereich, M.D.

Administrative Assistant

Ron Stein

Assistant Editor for Housestaff

Leora Horwitz, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

Scott H. Barnett, M.D.
J. Hugh Baron, D.M.
David H. Bechhofer, Ph.D.
Constantin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Donald Brief, M.D.
Daniel Buchbinder, D.M.D, M.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., M.P.H., M.P.P.
William H. Constad, M.D.
Kenneth L. Davis, M.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Jack Hirschowitz, M.B., Ch.B.
Fred M. Jacobs, M.D., J.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M. Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkovitz, M.D.
Dana M. Lewis, M.L.S.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Myron Miller, M.D.
Richard Panush, M.D.
Barbara E. C. Paris, M.D.
Jerome G. Porush, M.D.
Georges R. Ramalanjaona, M.D., D.Sc.
Veronica Ravnikar, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Tibor Rohacs, M.D.
Gregory J. Rokosz, D.O., J.D.
Joshua Rosenblatt, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Harry Schanzer, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Janet B. Serle, M.D.
Phyllis Shaw, Ph.D.
Scott H. Sicherer, M.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson N. Stone, M.D.
Max Sung, M.D.
Jules A. Titelbaum, M.D.
Thomas A. Ullman, M.D.
Richard P. Wedeen, M.D.
Klaudiusz R. Weiss, M.D.

Editorial Board

Barry S. Coller, M.D.
Kenneth L. Davis, M.D.
Panayotis G. Katsoyannis, Ph.D.
Jack G. Rabinowitz, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, Septemb October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-65 Subscription price: individuals (U.S. and Canada), $79 per year; libraries and institutions (U.S. and Canada), $121 per year; individuals (outs U.S. and Canada), $105 per year; libraries and institutions (outside U.S. and Canada), $147 per year. The charge per copy of a single num issue is $25, for a two-number issue is $50. New subscriptions begin with the first issue of the calendar year. Send notice of change of addr 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send addr changes to *The Mount Sinai Journal of Medicine*, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212) 2 6108. Fax (212) 722-6386. e-mail: msjournal@mssm.edu; web page: www.mssm.edu/msjournal. Copyright 2003.

DISCLAIMER: The statements and opinions expressed in *The Journal* by authors and contributors are solely their own and not those of The Mount Medical Center or *The Mount Sinai Journal of Medicine*. All advertisements are expected to conform to ethical standards, and their appearance does not in endorsement or approval by The Mount Sinai Medical Center and/or *The Mount Sinai Journal of Medicine* of the products with respect to effectiveness, qualit safety. The Mount Sinai Medical Center and *The Mount Sinai Journal of Medicine* do not hold themselves responsible for statements made by the autho contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in *The Journal* is protected by copyright. In accord with U.S. Copyright law, no part of *The Journal* may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior writt permission to do so. Permission should be requested from The Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 1094 One East 100th Street, New York, NY 10029-6574

Introduction

Daniel A. Moros, M.D.

Associate Professor of Neurology

Rosamond Rhodes, Ph.D.

Professor of Medical Education

Director, Bioethics Education

Lewis Burrows, M.D.

Professor of Surgery

Issues in Medical Ethics

THERE HAS BEEN A DRAMATIC IMPROVEMENT in transplant patient and graft survival over the past two decades. As a result, transplant technology has been extended to patients with liver, pancreas, small intestine, and lung end-stage organ failure, and more and more patients are opting for this form of therapy. Newer, safer and more powerful immunosuppressants, better anesthesia, new surgical techniques, and a better understanding of the immunological phenomena involved in the process have all contributed to this improvement.

The success of organ transplantation has led to two further developments. One is that physicians now consider extending transplantation to "quality of life" conditions that have not previously been considered amenable to transplantation. When significant risks were associated with organ transplantation and post-transplant immunosuppression, transplantation was reserved as the treatment of last resort for patients who would die without it. Now it is being considered as a treatment for patients who could survive without having a transplant.

The other consequence of the successes in transplantation is a persistent and continuing shortage of organs. As new patients turn to transplantation to extend their lives, and previous organ recipients outlive the viability of their transplanted organs and return for retransplantation, there is increased need and demand for organs from the cadaver pool. Although attempts to increase the supply of cadaver organs have been somewhat successful, there are still not enough to satisfy this growing demand. About five thousand patients on American waiting lists die each year as a result of this shortfall (1) . The severe shortage of human organs for transplantation has persuaded some transplant programs to introduce living donor transplantation.

Using living donors to provide organs for transplantation and extending organ transplantation technology to improve quality of life raises troubling new ethical issues. In designing the Mount Sinai School of Medicine's annual conference, "Issues in Medical Ethics," for 1999, and in publishing this collection as proceedings of that conference, we chose to focus on bringing some light to these controversial and challenging ethical issues.

The first group of papers in this special section addresses new domains for transplantation, some already being offered, others under investigation, and others at the stage of hypothetical possibility. In his paper "Extension of Organ Transplantation: Some Ethical Considerations," philosopher George J. Agich examines the question of whether the vital/non-vital distinction should mark the boundary for acceptable transplantation, and what additional considerations should be taken into account when deciding whether the risks associated with a transplant are justified. His paper is followed by discussions of several possible extensions of transplantation and the questions that each application would raise.

Dr. Albert Altchek considers the possibility of uterus transplantation. He explains the kinds of medical and emotional situations that create the need for such a procedure and elaborates on the factors that would make uterus transplantation unique: The transplant and the associated immunosuppression could be time-limited by reproductive goals rather than be lifelong; technical issues associated with providing a blood supply and managing rejection could be especially complicated; and the study of the uterus's response to foreign fetal tissue could provide an opportunity to learn about immunization and rejection.

Dr. Steven Fruchtman discusses stem cell transplantation. Although this procedure is already a well-accepted treatment for leukemia, an otherwise fatal disease, Dr. Fruchtman raises questions about the risks and harms to which donors are subjected, and other problems associated with the procedure. He also introduces questions about extending the procedure, with its inherent risks, as a treatment for thalassemia and sickle cell disease, conditions that are serious, but not immediately fatal.

Drs. Eric M. Genden and Mark Urken's paper deals with the possibility of laryngeal and tracheal transplantation. The authors describe patients with life-threatening thoracic tracheal defects, as well as patients who suffer the severe social handicap associated with laryngectomy. They also describe the special problems of revascularization and immunosuppression that would accompany these transplants, and the scientific advances that could make the procedure more feasible.

Drs. Michael R. Hausman and John Masters's contribution focuses on the much publicized issue of hand transplantation. They argue that the current risks associated with immunosuppression and the current low level of function that can be provided by a hand transplant, along with the psychosocial ramifications, render unjustified the procedure except for a very few exceptional cases.

The final pair of papers and the transcript of the panel discussion address the demanding decisions associated with living donor transplantation. Using living donors to provide organs for recipients produces no medical benefit for the donors, and subjects healthy people to certain disfigurement and the risks of harm and death. Nonetheless, a donor's commitment to a recipient can make the decision reasonable and acceptable from the donor's perspective. Yet the question remains of how to determine when transplant surgeons are justified in accepting the sacrifice of one person for the benefit of another.

Dr. Myron Schwartz raises the pressing issue of living donation in the context of liver transplantation. His discussion focuses on the issues of whether the urgency of the recipient's need justifies easing the standards for living donation, or whether the low likelihood of a good outcome for a recipient justifies raising the bar, or whether the donor's choice should always rule. Inherent in these ethical dilemmas is a broader question of whether autonomy should rule or whether medicine has the responsibility to set limits on living donation.

Philosopher Rosamond Rhodes uses the concept of trust to addresses the issues raised by Dr. Schwartz. She explains how the need for trust in the profession of medicine and in the programs that conduct living donation transplantation can be used to set the rules and moral boundaries for such programs.

Taken together, the papers in this section illuminate the unique and complex ethical challenges associated with recent developments in organ transplantation. The contributions, from physicians and philosophers, illustrate the medical, psychological and social problems that create the need to extend transplantation technology. They also highlight some of the complicated medical problems that must be surmounted in order to make transplantation an acceptable solution to these human needs and problems.

Reference

1. United Network for Organ Sharing (UNOS), 1999 Annual Report to the U.S. Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data 1999–2000. Rockville, MD and Richmond, VA: HHS/HRSA/OSP/DOT and UNOS; http://www.ustransplant.org/annual.htm; follow link labeled "Data by Organ" and then choose "All Organs 1.7"

Extension of Organ Transplantation:

Some Ethical Considerations

George J. Agich, Ph.D.

Abstract

The concept of vital organ transplantation is critically analyzed by considering how traditional transplantation modifies the commitment to saving lives. Problems such as those associated with immunosuppression might seem to provide a compelling reason to oppose extension of transplantation to non-lifesaving situations. A closer examination, however, shows that immunosuppression does not present an intractable objection. For some organ transplants, such as the uterus, use of immunosuppression could be limited to the childbearing years. Complexities associated with assessment of quality of life are discussed using the example of hand transplantation. Assessment of success and functionality in a hand transplant is more complicated than it might appear at first. These complications suggest that monitoring and assessment should be a part of any extension of organ transplantation. Informed consent provides a limited, but important, component in justifying extended transplantation. Such justification, however, does not rest on patient autonomy, but on the reasonable prospect of benefit. Transplant programs considering an extension of traditional transplantation should develop formal protocols that include assessment of costs, benefits, quality of life, and the adequacy of informed consent.

Key Words: Ethics, organ transplantation.

SUCCESS IN THE TRANSPLANTATION of solid organs such as kidneys, livers and hearts has led to discussion of expanding the types of organs that are candidates for transplantation. This paper discusses the extension of transplantation to include organs that are not necessary to sustain human life. These so-called "non-vital" organ transplants, for example, hand, larynx and trachea, stem cell, and uterus, seem to move transplantation into a new dimension. Rather than organ replacements that are directly lifesaving, these transplants aim instead at enhancing the quality of life of recipients. How can such extension of organ transplantation be justified ethically?

Three considerations that are essential to the justification of traditional organ transplantation, namely, cost benefit, quality of life, and informed consent, are also relevant to the ethical justification of extending transplantation to include other organs. A review of these considerations does not reveal any insurmountable objections to the extension of transplantation. However, a full justification of extended transplantation must apply these considerations to each particular organ. Thus, analysis of the individual organ and specific clinical situations for which the extension of transplantation is proposed is needed for the proper application of cost-benefit, quality-of-life, and informed-consent concerns.

The Vital/Non-vital Distinction and the Ethics of Rescue

Organ transplantation has been fraught with controversy, including the high cost and difficulty of securing an adequate number of organs

---

F. J. O'Neill Chair in Clinical Bioethics and Chairman, Department of Bioethics, Joint Appointment, Transplant Center, Cleveland Clinic Foundation, Cleveland, OH and Professor of Clinical Medicine, Department of Medicine, Ohio State University, Columbus, OH.

Address correspondence to George J. Agich, Ph.D., F. J. O'Neill Chair in Clinical Bioethics and Chairman, Department of Bioethics, Joint Appointment, Transplant Center, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

Presented at the Issues in Medical Ethics 1999 Conference at the Mount Sinai School of Medicine, New York, NY on December 10, 1999, and updated as of January 2002.

to meet the existing need (1). Extension of transplantation to include new organs that do not directly support a patient's life might seem ethically problematic in light of the continuing transplantation crisis. It might seem that the transplantation community should direct its energies toward solving the organ donation problem before embarking on an expansion of transplantation to other organs. A critic might argue that transplantation of new organs seems motivated by the economic needs of transplant programs that are confronting the limited availability of "traditional" organs. The critic might insist that extended organ transplantation would meet the economic needs of programs and health care institutions, rather than the needs of patients.

Underlying such criticism is the belief that the ethical obligation of the transplantation community is to increase the number of traditional organ transplants, because these organs are directly lifesaving. The goal of saving lives is given primacy and is seen as the overriding goal justifying the entire transplantation enterprise. Extending transplantation to organs that do not directly meet vital needs, therefore, would appear to be less ethically compelling. The risk associated with extending transplantation to organs that are not directly lifesaving is that such extension might compromise the ethical legitimacy of the entire transplantation enterprise and could ultimately adversely affect organ donation. In this view, if transplantation were to be extended to other organs, it would have to serve another purpose besides directly saving lives. As such, it would be perceived to be less ethically compelling and less worthy of public trust and support. Organ transplantation enjoys public trust, because it traditionally serves the ethically compelling goal of saving lives.

The belief that the goal of life saving is essential to the ethical justification and public acceptance of traditional organ transplantation rests upon the strongly felt need for a compelling response to the social ambivalence about organ procurement. A strongly valued goal, such as restoring basic physiological functions essential for life, is required to warrant the desecration of a corpse and the removal of organs. Traditional organ transplantation was based solidly on the ethics of rescue that permits exceptional efforts to be undertaken to save lives that are in immediate danger (2).

In situations in which individuals are at risk of death because of accident or other adverse event, the rescue ethic holds that the cost or other considerations that would argue against intervention can be overridden by the urgency of need. The rescue principle justifies the extravagant use of resources that would otherwise not be provided to individuals except when their lives are imminently at risk. The classic paradigm cases of organ transplantation, for example, for fulminant liver failure, hepatorenal syndrome, or end-stage congestive heart failure, clearly meet the requirements associated with this ethic.

Although such a rescue orientation imbues traditional organ transplantation, such requirements seem to have been necessary to overcome a deep social aversion to organ donation. It is undoubtedly true that some (perhaps even the majority of) transplants directly and immediately save lives, yet it is a mistake to conclude that transplantation can only (or primarily) be justified in terms of rescue. Traditional organ transplantation actually aims at a set of goals that is broader than rescue; it is guided by considerations of cost saving and quality of life in addition to lifesaving. These goals are essential elements in the full ethical justification of traditional organ transplantation, although they receive little attention in the characterization of transplantation in the public media. Yet the common practice of transplanting a kidney when dialysis is still an option is ethically justified not in terms of rescue, but on cost-savings and quality-of-life enhancement grounds (3). Recent work suggests that there is a growing tendency to place healthier patients on the waiting list for kidney transplantation (3, 4), based on the belief that transplant affords a better quality of life than chronic hemodialysis. Of course, transplantation might still reduce mortality (5), but it would be a mistake to think that the justification of kidney transplantation is primarily based on rescue. To say this is not to say that traditional transplantation of heart, liver, or kidney does not directly save patient lives, but only that saving life is only one element among a set of considerations involved in the ethical justification of transplantation.

It is widely agreed that use of a scarce resource such as a heart for transplant to an end-stage congestive heart failure patient with concurrent end-stage metastatic melanoma is not ethically justified, even though the heart transplant would itself be immediately lifesaving. Rather, such a transplant is not justified because the relative benefit that it would offer the patient, who is dying, is minimal. Organ transplantation requires not just general ethical justification, but a specific justification in light of the particular organ and clinical situation involved. Patients usually do not receive a transplant at the precise time when the transplant would be most evidently lifesaving (5), because at that point a patient may be too sick to derive a full measure of benefit from transplantation. Simply put, the scarce resource could be put to better use in a relatively stable patient whose quality of life might be greatly improved following the transplant. Even if the organ graft were successful and the underlying physiological function restored to the aforementioned end-stage patient with congestive heart failure, it would not change the ultimate clinical course. Such cases help us to recognize that replacement of a vital physiologic function cannot be the core ethical justification of organ transplantation. For this reason, it would be a mistake to begin a discussion of extended organ transplantation by assuming the ethical primacy of lifesaving for organ transplantation.

Transplantation is justified if the life is worth saving. Being "worth saving" is used in this context in two different senses: first, in the sense of life being extended, to be sure, but, second, in the sense of enhancing the quality of the life being saved. In the classic cases of rescue, we are not in a position to know or predict with high degrees of confidence that the outcome will be acceptable. Committing resources in rescue involves a significant degree of hope. However, with greater knowledge or experience, a more selective rescue effort can be ethically justified. For this reason, the ethic of life saving prohibits vain efforts.

Organ transplantation is ethically justified only in situations in which there is an acceptable relationship between cost and benefit and in which it is reasonable to expect that an acceptable quality of life can be attained. Because organs are scarce and transplantation costs are high, selection of the best candidates is an ethically important aspect of transplantation. To be ethical, transplantation should maximize not only graft or recipient survival, but also recipient's well-being. Survival under seriously compromised conditions is not a justified goal of organ transplantation. Rather, attainment of a satisfactory quality of life is a necessary element in the ethical justification of transplantation. If the recipient's quality of life were less during the post- transplant than during the pretransplant period or it were otherwise unacceptable for the patient, transplantation would not be justified. These considerations strongly suggest that extension of transplantation to organs that do not directly save a life can be ethically justified if they favorably meet cost benefit and quality of life outcome standards. The ethical justification of programs to extend transplantation to new types of organs will thus need to address these concerns.

The ethical relevance of cost and benefit considerations to transplantation is especially evident in cases in which traditional organ transplantation is offered to patients who have less than urgent need. For example, patients who are not refractory to dialysis cannot receive kidney transplantation based on direct lifesaving alone since another life-sustaining treatment for end-stage renal disease is also available. Rather, kidney transplantation has been extended to such patients based on economic-cost and quality-of-life considerations (5–8). Data from other types of transplantation also shows that quality of life post-transplant is significantly improved (9–12). This point makes it clear that lifesaving alone is not the main ethical justification for organ transplantation, because cost/benefit and quality of life have an important role to play even in traditional organ transplantation. So, how might considerations of cost, benefits, and quality of life function in the ethical assessment of programs to extend transplantation to new organs?

Cost/Benefit and Quality-of-Life Considerations

One significant and common cost associated with extended organ transplantation involves the need for lifelong immunosuppression. Dependence on immunosuppression is an ethically significant consideration especially when the transplant does not directly maintain life, because it exposes the recipient to risks of infection, cancer, diabetes and other complications associated with immunosuppression that cannot be lightly dismissed (13, 14). Programs to extend transplantation will need to consider the risks and benefits of immunosuppression in terms of the specific organ and not rely on general inferences from the broad transplant literature. For some types of extended transplantation, immunosuppression poses unique challenges. For example, cyclosporine is known to cause peripheral neuropathy (13, 15). In the case of a hand transplant, attaining fine motor skill and sensory awareness is an essential part of a successful hand transplant (16–19), but cyclosporine may lessen the chance of achieving a satisfactory post-transplant experience.

Not every type of extended transplant, however, poses a lifelong immunosuppression risk as do traditional organ transplants. For example, transplantation of a uterus primarily for childbearing would not incur the risks associated with lifelong immunosuppression if the patient accepted a post-partum hysterectomy. In this case, the risks and benefits associated with immunosuppression could be limited to the pre-pregnancy and pregnancy periods. Although use of immunosuppression would be relatively short term, the risk assessment would also need to include potential adverse effects on the pregnancy itself. Concern about the risks of immunosuppression, however, have to be placed within the context of known evidence about quality of life and known risks of chronic immunosuppression. Literature on heart, liver, and kidney transplants indicates that quality of life remains high after transplantation, even approaching the normal range (9, 11, 12). Whether immunosuppression usage in extended organ transplantation will lead to different outcomes is unknown.

To illustrate how these considerations function in the ethical assessment of extended transplantation, we turn to the case of hand transplantation (20, 21). Ethically, the cost and benefits of the transplant would have to be weighed against the functional and esthetic qualities of available prostheses. Technological developments promise even further improvements in prosthetic function, cost, and acceptability by patients. That said, a prosthesis is not a human hand, so the desire for a "natural" hand is understandable. This desire has to be analyzed to see its full ethical import. Complex judgments need to be made about the benefits and functions of a prosthesis versus a transplant in light of the costs.

First, the hand is an external organ, so its esthetic qualities as well as its functional capability are important. Beyond the usual considerations of blood and HLA matching, selection of a hand for a particular recipient would have to match, among other things, the size, shape, and skin tone of the other hand. Consideration of the appearance of the "organ" is unique to this form of organ transplantation. Second, the functional capability of the transplanted hand has to be analyzed not only in terms of objective measures, but also in terms of how the transplant is experienced by the recipient. The recipient's own subjective evaluation of the graft's function in the myriad activities of daily living is crucial in this assessment. A graft that might not perform better than a prosthesis in grasping, nonetheless, might confer significant benefit on a patient if it afforded sensory awareness. Similarly, a graft that performs significantly better than a prosthesis might still be experienced as problematic if it did not provide a suitable range of sensory input. Restoration of the full range of sensation characteristic of the normal hand is a complex and possibly elusive goal for hand transplantation. An ethical prerequisite for undertaking hand transplantation is the development of a program to assess the restoration of sensation and the effect of the transplant on the patient's quality of life.

Philosophical textbook discussions of organ transplantation often rely on a stock example of transplanting a hand to a concert pianist. The classic use of this example is to argue that transplantation is justified based on the importance of the hand to the individual. Unfortunately, these textbook discussions seldom consider the sensory, physiological, or functional complexities associated with a composite organ like the hand. The hand must be innervated in such a way that something approximating normal sensation and movement is possible. Experience with replantation of severed hands has shown that reattaching a severed hand cannot always achieve the degree of functionality of the pre-injury hand (17, 22–24). It is possible that even the most technically successful hand transplant would not provide the idealized restoration of performance dexterity and associated sensory capacities that are assumed in the concert pianist's example.

If functionality were not accompanied by adequate sensation, the hand might not provide better service than a prosthesis. A prosthesis can certainly be damaged, but a hand that lacked the protective sensation of heat or pain would be susceptible to myriad types of injury that could ultimately affect the health of the patient. Such injuries would not be limited to the hand alone, but could affect the entire body, for example, through infection. Experience with replantation, that is, reattachment of a patient's own severed hand, has shown that restoration of sensation is critically important to the acceptance of the graft by the patient (22). Thus, the desire of the recipient to have a "natural" hand may be even more difficult to achieve when the hand is not perceived as the patient's own. The hand, like the larynx, is a communicative tool that is integral to the person's status as an agent in the world. The hand is unlike other organs, because it is in the world as a perceived object, yet it is also a sensory organ of the person. Being in the world, it allows the person to contact things and other persons. In touching, the hand allows the person to sense the properties, surface texture, hardness, density, or temperature of objects. In touching, the hand also communicates with objects. A hand can slap, hit, or caress. It can itself shape things in the world and, so, remake the things into new forms. We also rely on the uniqueness of the hand as an individuating marker; for example, fingerprints are used to establish the identity of individuals.

A hand that is not fully functional, that is not esthetically satisfactory to the recipient or the recipient's significant others, or that cannot provide the sensory nuances that are so important to the everyday function of a hand may create serious psychological burdens and frustrations that are not encountered in other types of transplants (23). Such outcomes might significantly diminish the quality of life after transplantation. Understanding and assessing the full functionality of the hand and the costs and benefits associated with its transplantation thus turns out to be much more complex than understanding the functions that a liver or heart transplant replace.

This line of analysis suggests that while the consideration of costs, benefits and quality of life are complex in extended transplantation, they do not provide formidable ethical reasons to oppose such transplantation. In fact, the discussion suggests that the ethical justification of extending organ transplantation is possible if sufficiently compelling evidence or arguments can be developed, on an organ-specific basis, to answer the kind of questions being raised. Some considerations, such as the risk of rejection and the complications associated with immunosuppression, are universal, but their ethical salience, too, will vary from organ to organ. Ethically responsible programs that extend transplantation to new organs will identify and address these elements. Such assessment is important both to justify beginning a program and to responsibly carry it out.

A degree of caution is justified, because the cost and benefits in situations of true innovation are somewhat speculative. It is unclear, for example, how having one's own voice will be accepted by the recipient of a larynx transplant if that voice is not experienced by self or others as his or her own. In other words, because a voice has a distinctive character and aural quality, acceptance and adjustment will be necessary. It is unclear whether recipients and their significant others will accept or adjust to the new voice, but the report of the first laryngeal transplant is that the recipient's quality of life has immeasurably improved (25). The experience with replantation of severed hands indicates that significant rehabilitation is necessary before functional abilities are regained (26–30), including the patient's ability to adapt to the demands of rehabilitation, to accept setbacks and slower than hoped-for progress, and to expend the effort required to make the transplant a success. Whether programs can adequately address these concerns is an empirical question, but there are no significant technical impediments. Programs extending transplantation into these new areas should be conducted under protocols that provide for ongoing assessment of quality-of-life outcomes.

Informed Consent

Those who would give autonomy a central place in bioethical considerations often take the position that informed consent is the central ethical standard for medical decision making. Consent contains two distinguishable functions that are often overlooked: authorization and legitimation. In giving consent, a patient provides permission and thereby authorizes the health professional to perform the procedure. Ethically valid permission depends on adequate disclosure of information relevant to the decision. This aspect of consent underlies the well-recognized obligation of physicians to disclose risks, benefits, and alternatives to patients. In some interpretations, in fact, the doctrine of informed consent is epitomized in the physician's obligation to disclose information. The agreement of the patient simply provides permission.

Other interpretations provide a richer understanding of the patient's informed consent. After being provided with relevant information, the patient is allowed to consider the proposed treatment and to judge whether it comports with his or her personal values, beliefs, or preferences. In the act of consenting, a patient not only authorizes treatment, but also provides an ethical justification for the treatment. In this view, the informed consent of an autonomous person legitimates the procedure or intervention. This legitimation function of consent can provide the ethical justification for extended transplantation. So long as full disclosure of risks and benefits occurred and informed consent was obtained, the extension of transplantation to new organs would be justified ethically. This interpretation gives informed consent considerable ethical weight. Even if prospective recipients are enthusiastic and would accept transplantation after being fully informed, this focus on patient autonomy constitutes an ethically inadequate approach to the extension of transplantation services. Such a strong interpretation gives informed consent too much weight, thus slighting other considerations.

Central among the other ethical considerations that balance autonomy considerations are the professional obligation of beneficence and the corollary of minimization of harm, core values that define medicine as an ethical practice (31). The functions of authorization and legitimation provided by informed consent operate within the normative framework of the physician-patient relationship. Within this relationship, there is congruence between the patient's goal of regaining health and the physician's professional commitment to patient well-being. The professional commitment to beneficence is grounded in the professional competence to practice medicine. Traditional professional ethics, however, were based not only on the personal commitment of physicians to benefit their patients, but also on the scientifically derived professional knowledge that assures a beneficial outcome. Extension of medicine beyond these standards, however, raises serious ethical questions that are not adequately answered by appeal to the principle of patient autonomy alone.

Illness makes patients vulnerable and they might consent to interventions that impose undue risk or burdens. Their vulnerability remains even if they receive the fullest disclosure of risks and alternatives. For this reason, even if coupled with informed consent, the desire for (and consent of patients to) transplantation of organs such as hand, larynx, or uterus, is an ethically incomplete basis for justifying programs to extend transplantation. Although individuals may be willing to undertake a risk, it is ethical to subject them to it only when the benefits are reasonable and consistent with the goals of medicine.

Considerations of cost, benefits, and quality of life provide an analytical framework for medicine's obligation to expose patients to risk only when the potential benefit is acceptable. The obligation of transplant programs, like the professional ethical obligation of individual physicians, is to pursue courses of action that have a reasonable basis for enhancing or restoring patient welfare. In this view, respect for patient autonomy is balanced by the professional judgment that the risks associated with extended transplantation are worth undertaking in light of the potential benefits to be achieved. Beneficence can be sacrificed if transplant programs are extended primarily in response to patient demands. Even if they are motivated by compassion and a desire to alleviate the suffering of patients from conditions like Rokitansky's syndrome or the loss of voice resulting from laryngeal carcinoma, the decision to extend transplantation services requires a broader ethical justification.

Given the uncertainties associated with the extension of transplantation, informed consent will exert its strongest justificatory force only when transplantation is extended under the banner of investigation, rather than clinical practice. Innovation, however, demands an even wider range of considerations than cost, benefit, quality of life, and informed consent. To be ethically justified, innovation must be undertaken responsibly, which entails three further considerations. As described by Francis Moore, responsible innovation in medicine rests on the adequacy of the scientific background upon which the procedure is based, the skill or experience — the "field strength" — of the team performing the procedure, and the ethical climate of the institution itself (2, 32). While the first two elements are significant, Moore stresses the third, noting how economic motivations can sully judgment (2). The ethical assessment of the financial motivation to extend transplantation can be addressed by seeking review and advice from the institution's ethics committee or other body charged with addressing organization ethics.

Summary

The reliance on cost/benefit considerations in the ethical justification of extending renal transplantation to patients who are not refractory to dialysis, and therefore not immediately in need of rescue, provides an important analogy for thinking about extending transplantation to new organs. Cost/benefit considerations and quality of life have an ethically important function in justifying the extension of transplantation. Such justification, however, must involve an organ-specific ethical assessment. Such evaluation should be delineated in a formal protocol with the involvement of professionals with appropriate experience and training in the design, implementation, and evaluation of the program. The protocol should identify specific inclusion and exclusion criteria, and include provisions for data collection, and ongoing assessment and monitoring of medical and psychosocial risks, complications, and adverse events, as well as assessment of outcomes. The scientific basis for extending transplantation should be strong and the team or program should possess appropriate competence and experience in transplantation. Finally, the program and institution should critically evaluate their own motives for wanting to extend transplantation, because institutional and program self-interest can corrode the complex processes required to extend transplantation responsibly.

References

1. Institute of Medicine Committee on Organ Procurement and Transplantation Policy. Organ procurement and transplantation: Assessing current policies and the potential impact of the DHHS final rule. Washington (DC): National Academy Press; 1999.
2. Moore FD. Three ethical revolutions: ancient assumptions remodeled under pressure of transplantation. Transplant Proc 1988; 20(1 Suppl 1):1061–1067.
3. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 341(23):1725–1730.
4. Port FK, Wolfe RA, Mauger EA, et al. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA 1993; 270:1339–1343.
5. Hunsicker LG. A survival advantage for renal transplantation. N Engl J Med 1999; 341(23):1762–1763.
6. Wicks MN, Milstead EJ, Hathaway DK, et al. Family caregivers' burden, quality of life, and health following patients' renal transplantation. J Transpl Coord 1998; 8(3):170–176.
7. Rebollo P, Ortega F, Baltar JM, et al. Health-related quality of life (HRQOL) in end stage renal disease (ESRD) patients over 65 years. Geriatr Nephrol Urol 1998; 8(2):85–94.
8. Matas AJ, Gillingham KJ, Payne WD, et al. A third kidney transplant: cost-effective treatment for end-stage renal disease? Clin Transpl 1996; 10:516–520.
9. Price CE, Lowe D, Cohen AT, et al. Prospective study of the quality of life in patients assessed for liver transplantation: outcome in transplanted and not transplanted groups. J R Soc Med 1995; 88:130–135.
10. DiMartini A, Rovera GM, Graham TO, et al. Quality of life after small intestinal transplantation and among home parenteral nutrition patients. JPEN J Parenter Enteral Nutr 1998; 22(6):357–362.
11. Bryan S, Ratcliffe J, Neuberger JM, et al. Health-related quality of life following liver transplantation. Qual Life Res 1998; 7:115–120.
12. Molzahn AE, Burton JR, McCormick P, et al. Quality of life of candidates for and recipients of heart transplants. Can J Cardiol 1997; 13(3):141–146.
13. Miles AM, Sumrani N, Horowitz R, et al. Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes? Transplantation 1998; 65(3):380–384.
14. Winter P, Schoeneich G, Miersch WD, et al. Tumour induction as a consequence of immunosuppression after renal transplantation. Int Urol Nephrol 1997; 29(6):701–709.
15. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol 1999; 246(5):339–346.
16. Kann BR, Furnas DW, Hewitt CW. Past, present, and future research in the field of composite tissue allotransplantation. Microsurgery 2000; 20(8):393–399.
17. Lee WP. Composite tissue transplantation: more science and patience needed. Plast Reconstr Surg 2000; 107(4):1066–1070.
18. Lee WP, Mathes DW. Hand transplantation: pertinent data and future outlook. J Hand Surg [Am] 1999; 24(5):906–913.
19. Owen ER, Dubernard JM, Lanzetta M, et al. Peripheral nerve regeneration in human hand transplantation. Transplant Proc 2001; 33(1–2):1720–1721.
20. Dickenson D, Hakim NS. Ethical issues in limb transplants. Postgrad Med J 1999; 75(887):513–515.
21. Siegler M. Ethical issues in innovative surgery: should we attempt a cadaveric hand transplantation in a human subject? Transplant Proc 1998; 30:2779–2782.
22. Shieh SJ, Chiu HY, Hsu HY. Long-term effects of sensory reeducation following digital replantation and revascularization. Microsurgery 1998; 18(5):334–336.
23. Fukunishi I. Relationship of cosmetic disfigurement to the severity of posttraumatic stress disorder in burn injury or digital amputation. Psychother Psychosom 1999; 68(2):82–86.
24. Boulas HJ. Amputations of the fingers and hand: indications for replantation. J Am Acad Orthop Surg 1998; 6(2):100–105.
25. Strome M, Stein J, Esclamado R, et al. Laryngeal transplantation and 40-month follow-up. N Engl J Med 2001; 344(22):1676–1679.
26. Cooney WP, Hentz VR. Successful hand transplantation — one year follow-up. N Engl J Med 2001; 344(1):65.
27. Jones JW, Gruber SA, Barker JH, Breidenbach WC. Successful hand transplantation. One-year follow-up. N Engl J Med 2000; 343(7):468–473.
28. Francois CG, Breidenbach WC, Maldonado C, et al. Hand transplantation: comparisons and observations of the first four clinical cases. Microsurgery 2000; 20(8):360–371.
29. Dubernard JM, Owen E, Lefrancois N, et al. First human hand transplantation. case report. Transpl Int 2000; 13(Suppl 1):S521–S524.
30. Dubernard JM, Owen ER, Lanzetta M, Hakim N. What is happening with hand transplants. Lancet 2001; 357(9269):1711–1712.
31. Pellegrino ED, Thomasma DC. For the patient's good: the restoration of beneficence in health care. New York and Oxford: Oxford University Press; 1988.
32. Moore FD. Therapeutic innovation: ethical boundaries in the initial clinical trials of new drugs and surgical procedures. CA Cancer J Clin 1970; 20(4):212–227.

Hand Transplantation:

Current Status

Michael R. Hausman, M.D.[1], John Masters, M.D.[2], and Albert Panozzo, M.D.[3]

Abstract

The hand is a very special organ, with unique functions and versatility in the human body. Our hands are pivotal in manipulating our environment, receiving feedback from our surroundings and communicating our unspoken words by gestures. Thus, the loss of a hand is a tragic, disfiguring event with profound personal, vocational, financial and social implications. Transplantation of life-saving solid organs is now widely accepted in both the medical and lay communities. The technical skills and prerequisites for hand transplantation have been honed over recent decades, culminating in the recent commencement of hand transplantation in several centers around the world. However, unlike life-saving solid organ transplantation, hand transplantation has been greeted with less enthusiasm in the professional community because it is not yet clear what the long-term risks-to-benefits ratio is. The scientific background, and the potential risks, benefits, and ethical aspects of this procedure are discussed. Successful transplantation to amputees of fully integrated and functional hands is a worthy goal. Hopefully, at some point in the future, hand transplantation will become another safe and viable option for amputees to consider.

Key Words: Transplant, ethics, hand, hand transplant.

THE HAND IS A VERY SPECIAL ORGAN. Its level of function and versatility is unique, in that it requires an integration of sensory input and fine motor control not found anywhere else in the body. The sensibility of the hand is vital. It is disproportionately represented in the brain, indicating the degree of its importance. Our hands are pivotal in manipulating our environment, receiving feedback from our surroundings and communicating our unspoken words by gestures. The hands have even been credited with being intimately involved in the development of language (1–3).

The loss of a hand is a tragedy; it is profoundly disfiguring, both physically and psychologically. The hand is an external organ that carries obvious emotional investment; people do not pine for the loss of a kidney as they do for the loss of a hand. For some, the loss of a hand represents the end of a vocation, for most it represents a reduction in their ability to support themselves and their families, and for all there is a profound distortion in their perceived personal body image. Successful transplantation of fully integrated and functional hands to amputees is a worthy goal. Hopefully, at some point in the future, hand transplantation will become another safe and viable option for amputees to consider.

Being a composite of multiple tissue types (including bone marrow) with differential immunogenicity, the hand differs significantly from traditionally transplanted solid organs, which have a relatively homogeneous parenchyma. The most significant difference, however, is that hand transplants are not lifesaving procedures. At best they may improve the recipients' quality of life, although some would argue this point. Unlike solid organ transplant recipients, amputees already have a range of optional prosthetic devices (aesthetic and functional) that can improve the quality

---

[1] Clinical Associate Professor of Orthopaedics and [3] Fellow in Hand Surgery, Mount Sinai School of Medicine, New York, NY; and [2] Reconstructive Plastic and Hand Surgeon, Plastic Surgical Masters, Auckland, New Zealand.

Address correspondence to Michael R. Hausman, M.D., Clinical Associate Professor of Orthopaedics, Box 1188, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Presented at the Issues in Medical Ethics 1999 Conference at the Mount Sinai School of Medicine, New York, NY on December 10, 1999. This paper has been updated as of December 2002.

of their lives without being potentially life threatening.

Whereas transplanted organs perform their specific physiological tasks without nervous integration, a transplanted hand needs to achieve cortical representation for both sensibility and fine motor control. Solid organ transplants continue to function "optimally" whether the recipient is aware of them or not. To be of value, however, hand transplants require the continual activity and consciousness of the recipient.

Although hand transplantation is not a lifesaving procedure, Moore's six criteria for assessing the ethical appropriateness of this innovative surgery are still relevant (4). According to Moore, transplantation is an ethically acceptable medical option only when all of these standards are met:

1. The scientific background of the innovation.
2. The skill and experience of the team.
3. The ethical climate of the institution.
4. Open display.
5. Public evaluation.
6. Public and professional discussion.

In our opinion, the first modern-era hand transplant, performed in 1998, failed to fulfill some of these criteria, particularly those of open display and public evaluation (5). Most commentators accept that the Louisville group, which performed the second hand transplant in 1998, met the latter five of Moore's standards (6). Only the scientific background of the innovation remains in question. Siegler (7) wrote, "the question is whether the equipoise consideration has been satisfied. Equipoise describes a situation of uncertainty in which the clinical investigator regards the potential outcome of an experiment or clinical trial as truly balanced between its potential for benefitting the patient or for causing unintended harms." Do we know enough about the potential risks and benefits of human hand transplantation to satisfy the question of equipoise? Needless to say, the true long-term risks and benefits that can be anticipated from this surgery are not known. We can, however, extrapolate from our experience with hand replantation, with a limited number of other non-solid organ allogenic transplants, and with traditional organ transplantation and animal limb/composite tissue transplant experimentation, to meaningfully discuss the likely results.

Relevant Experience

Malt performed the first upper extremity replantation at the Massachusetts General Hospital in 1962 (8). Shortly thereafter, Chen performed the first microsurgical hand replant (9). A successful hand replant depends upon the level of amputation, maximizing tissue survival and restoration of function, i.e., "survival without restoration of function is not success" (10). Given that hand transplants will be performed in dedicated hand centers upon surgically amputated tissues (devoid of crush or avulsive injury), it is likely that initial revascularization, and hence tissue survival, will be successful (rejection issues will be discussed later). Outcome scoring systems for limb replantation have been applied to several case series reviews of replantations at the wrist or distal forearm (11). Good-to-excellent results occurred in 23–89% of the patients reported in five series with more than 10 patients. The more proximal the replantation, the worse the result that can be anticipated; fingertip replants do very well (12, 13). At the distal forearm level, two-point discrimination return is usually greater than 30 mm and most patients do not have protective sensation (14). Active range of motion is incomplete, about 28–38% of normal, and regaining intrinsic muscle function is the exception, not the rule (14). In our personal experience, every patient who had an immediate forearm amputation has returned to work, whereas everyone with forearm replantation has failed to return to work.

The advantages of planned execution (ideal circumstances for tissue transportation and cooling, pristine donor tissues, etc.) for initial limb revascularization may be offset by the recipient limb's loss of functional outcome secondary to chronic scarring, muscle atrophy and/or contraction. Additional unknown factors are the effects of immunosuppression and episodes of rejection (acute or chronic) upon functional outcome. It is reasonable to assume that the results of allogenic hand transplantation will be, at best, equivalent to the results of hand replantation (11).

There have been scattered reports of composite tissue allogenic transplantations in humans. Jones et al. (15) reported on the successful transplantation of a rectus abdominis muscle for scalp reconstruction in a renal transplant recipient, Guimberteau et al. (16) reported two cases of transplanted digital flexor tendon/tendon sheath complexes, and Hofmann et al. (17) reported on vascularized allogenic femoral diaphyseal and knee joint transplants (2 of 5 requiring removal for chronic rejection). Strome has transplanted a larynx (18). None of these composite tissue allogenic transplants included skin, a highly antigenic tissue that has repeatedly proven troublesome in animal experiments. The long-term results of these procedures are still unknown. Interestingly, immunosuppression was only given for six months to those patients with digital flexor tendon/tendon sheath transplants, and there have been no negative sequelae during the following six months, in which immunosuppression was not administered.

The results of animal experiments with allogenic limb transplants and composite tissue allogenic transplants are usually divided into small animal and large animal/primate groupings. Without immunosuppression, limb and composite tissue allogenic transplants are doomed to rejection, and most of the literature is devoted to trials of alternative immunosuppression regimes. Lee et al. (19) have shown that a different degree of antigenicity is present in the various components of a composite tissue graft. Additionally, the host immune mechanism responds to the different antigenic stimuli differently (e.g., muscle causes a greater cell-mediated response and skin a greater humeral response). Thus, it is likely that any successful immunosuppression regime will need at least two agents.

Cyclosporin has been extensively studied in the rodent model. Rejection-free survival of more than one year has been reported with cyclosporin alone (20). This was at the expense of high doses (8 mg/kg/day), and hence, there was associated morbidity. Other cyclosporin-only experiments have failed to replicate these results. Even with higher doses (15 – 25 mg/kg/day), early rejection was a problem. The outcomes of two rodent limb allograft experiments using FK-506 for immunosuppression also demonstrated longer-term survival at the cost of significant morbidity, primarily *Pneumocystis carinii* pneumonia (suggesting the development of graft-versus-host disease) and/or chronic mild-to-moderate signs of skin rejection (21).

Mycophenolate mofetil (MMF, RS-61443) successfully prevented rejection for 32 weeks in 5 of 6 rats with whole limb transplants. This group displayed restoration of sensory and motor function (22). MMF was then combined with low-dose cyclosporin, leading to 89% survival at 230 or more days (23). On this basis, combination therapy with low-dose cyclosporin and MMF has been proposed as an appropriate immunosuppression regime for allogenic transplantation.

Lance et al., using antilymphocyte serum, azathioprine and hydrocortisone combinations, and Goldwyn et al., using 6-mercaptopurine and azathioprine in canine hind limb allogenic transplant experiments, failed to demonstrate immune tolerance without significant drug toxicity (24, 25).

Three studies using primate models, which more closely resemble the human immune system and anatomy, have been published (26 – 28). Daniel et al. (26) transplanted four baboon hands and seven neurovascular-composite-tissue, digital-free flaps, using high-dose cyclosporin (trough levels > 1000 ng/mL) and methylprednisolone (4.4 mg daily) for maintenance immunosuppression. One hand remained in excellent condition 300 days after transplantation. The remaining three underwent various degrees of rejection: one was hyperacute, one was salvaged at two months from a severe rejection episode, and the fourth hand was lost secondary to an iatrogenic reduction in the cyclosporin maintenance dose followed by an infection. Electrophysiologic testing of the two long-term surviving hands showed motor, sensory and nerve regeneration. All seven composite digital flaps were technically successful; however, the first three showed signs of rejection, including edema, vesiculation, ulceration and epidermal sloughing.

Stark et al. also used a baboon model for the transplantation of eight hands, with cyclosporin (trough > 800 ng/mL) and prednisolone (5 mg daily) for immunosuppression (27). Six of the hands were lost in the first 15 days. Loss of the first hand, at two days, may have been due to a technical error, but the remaining five showed signs of acute rejection. The seventh hand was lost due to an anesthetic problem. The eighth hand survived 296 days before elective sacrifice; throughout this period there was evidence of chronic skin rejection. Of note were the findings of patchy lymphoplasmacellular infiltrates in specimens of the recipient's autologous tissue. The authors felt that these may have represented discrete areas of graft-versus-host disease and warranted further investigation.

The final study, by Hovius et al. (28) and Stevens et al. (29), reports using a Rhesus monkey partial-hand transplant model. Cyclosporin (25 mg/kg/day) and prednisone (1 mg/kg/day) maintenance immunosuppression was used. Acute rejection episodes were treated by either steroid dose increases or monoclonal antibodies specific for different surface antigens on immunocompetent cells. Ten of the 12 recipients had histologically confirmed rejection. In all cases, the skin was more rapidly rejected than were nerve and muscle. Rejection could not be reversed by increasing the steroid dose. Two of the five cases of rejection treated by monoclonal antibodies were successfully reversed on two occasions each. Significant immunosuppression side effects were encountered. One monkey died from irreversible shock after the first injection of monoclonal antibodies, three died from bacterial infections and three others died from lymphoid tumors. Additionally, autopsy revealed that one of the monkeys that died of sepsis also had a tumor. There was no correlation between cyclosporin trough levels and death by either sepsis or lymphoid tumor. The authors concluded that "a more effective, less toxic immunosuppressive regime is needed before actual allogenic transplantation of the hand should be performed in human patients, though it was demonstrated previously that it is technically feasible and that results for functional recovery are promising" (28).

Of particular interest are the two reports of porcine limb transplantation by Ustuner et al. (30) and Jones et al. (31), both using a radial forearm osteomyocutaneous flap model. The first study used cyclosporin (trough levels 100–300 ng/mL), MMF (500 mg daily), and prednisone (0.1 mg/kg daily) immunosuppression. Of the ten successful procedures, one pig died from pneumonia (day 19) and another from an anesthetic complication (day 30); neither pig had any signs of rejection. Two flaps were lost from severe rejection on days 25 and 29, respectively. Three flaps had mild-to-moderate rejection at day 90 (the study end point). The remaining three flaps were free of rejection at day 90, two of them having had an earlier episode of spontaneously resolving rejection. During the trial, two of the pigs developed pneumonia and one developed a wound infection. There were also two episodes of distant septic arthritis. The second porcine study (from the same group) used tacrolimus (FK-506, trough levels 3–8 ng/mL), MMF (500 mg daily), and prednisone (0.1 mg /kg daily) for immunosuppression. Three of the pigs died from pneumonia on days 29, 30, and 83. Four of the pigs developed early grade I-III rejection; three of these resolved, but the fourth died prior to healing from a gastric rupture on day 42.

Combining these two studies reveals that only 11 of 19 (58%) transplants survived the experiments, and that the mortality rate was 32% overall. None of the viable transplant recipients completed the experiment without at least one episode of rejection or sepsis. Later, in a paper reporting the first-year follow-up of their first hand transplant, Jones et al. state, with particular reference to these porcine experiments: "In these studies, however, drug doses were not adjusted according to the clinical progress of the animals, as would be done when humans are treated. Therefore, our decision to proceed with the tacrolimus-based regime for immunosuppression after human hand transplantation was based on the hypothesis that efficacy in preventing rejection and systemic toxicity could be balanced clinically" (6).

The consensus at the conclusion of a 1997 international symposium on composite tissue allotransplantation was that it was time to "just do it" (32). On Sept. 23, 1998, the distal right forearm of a 41-year-old donor was transplanted to a 48-year-old man in Lyon, France (5). Four months later, the first successful American hand transplantation was completed by the Louisville team (6). To date, fourteen hand transplants in eleven patients have been performed over the past three years (33). The first of these fourteen transplants was amputated for chronic rejection at 2 years and 4 months. The longest surviving transplant is now more than 3 years post surgery.

The initial functional outcomes of the first four human hand transplants have been published (34). The time to follow-up ranged from 8–20 months. Only the range of motion of the forearm and wrist is documented, but the results are better than would have been expected based on previous results of replantation of the hand and wrist. There has been electromyographic evidence of reinnervation of the intrinsic muscles of the hand. Sensory return, however, has been less than expected. Although all 4 patients showed progression of an advancing Tinel sign, Semmes-Weinstein sensory testing varied from between deep pressure sensation to loss of protective sensation to diminished protection sensation. Finally, the Carroll test of functional recovery (35), which integrates mobility, motor function, and sensation, was available for 3 of the 4 patients and ranged between 52 and 75, which translates to 1 good and 2 fair results.

The first American recipient has been able to return to work as a paramedic and perform duties he was previously incapable of, even with a prosthesis. A one-year follow-up paper has documented that (6):

1. he required anti-rejection intervention 3 times in the first 30 weeks,
2. he developed tissue-invasive cytomegalovirus infection at 15 weeks,
3. there is electromyographic evidence of innervation of the intrinsic muscles,
4. temperature, pain and pressure sensation is present in the fingers (no formal assessments were reported).

In an editorial in the *New England Journal of Medicine* (36), Herndon suggested that hand transplantations will most likely continue to be performed while we await the results of the procedures that were already performed. More basic research and safer immunosuppressive drugs are still needed. He poses the basic question about hand transplantation (36): "Should they be?" His suggestion, with which these authors agree, is to limit the procedure to patients who have lost both hands or who are already on immunosuppressive drugs for other reasons.

Additional Considerations

Lee and Mathes classify the risks associated with chronic immunosuppression into three categories: adverse effects of individual immunosuppressants, opportunistic infections and malignancy (11). The first French and American patients have all been prescribed tacrolimus, MMF and prednisone for their long-term immunosuppression. These drugs are not without dose-related risks, including nephrotoxicity, neurotoxicity, diabetogenicity, osteoporosis, bone marrow suppression and gastrointestinal toxicity. Historically, more than 80% of organ transplant recipients develop at least one infection after transplantation, and 40% of the deaths are due to infectious complications occurring alone or following rejection (11). The risk of malignancy associated with chronic immunosuppression in organ transplant recipients has been reported in the range of 4–18%. The incidence of malignancy relates both to the duration and extent of the immunosuppression.

In some of the animal experiments, there was evidence that a chimeric state had developed, in which functional immune components of both organisms coexisted, in a few of the more successful recipient-donor pairings. While this privileged state is beneficial when it occurs, the transplantation of immunocompetent T lymphocytes into an immunosuppressed recipient risks the development of graft-versus-host disease (GVHD). GVHD is the major complication of bone marrow transplantation and, as such, is a definite possibility with allogenic hand transplants. In broad terms, GVHD can be prevented by decreasing the number of donor T cells transplanted or by immunosuppressing the recipient after the transplant. As described above, the immunosuppressive regimes tested may have been insufficient to prevent the occurrence of GVHD despite significant recipient immunosuppression side effects.

Conclusions

Questions remain about the adequacy of the scientific background to human hand transplantation, particularly with regard to:

- what constitutes appropriate immunosuppression,
- the likelihood of infections,
- the possibility of malignancy and graft-versus-host disease,
- the likelihood of a fair-to-poor functional result of 11–76%,
- the lack of long-term successful animal transplantation without evidence of chronic rejection or systemic toxicity.

We believe that without more substantive evidence of an expectation for a good outcome, the procedure should be limited to patients who have lost both hands or who are already receiving immunosuppression for another reason.

References

1. Wilson FR. The hand: how its use shapes the brain. Language, and human culture. 1st ed. New York: Pantheon Books; 1998. Pp. xiv, 397.
2. Dunbar R. Grooming, gossip and the evolution of language. Cambridge (MA): Harvard University Press; 1996.
3. Donald M. Origins of the modern mind: three stages in the evolution of culture and cognition. Cambridge (MA): Harvard University Press; 1991.
4. Moore FD. Ethical problems special to surgery: surgical teaching, surgical innovation, and the surgeon in managed care. Arch Surg 2000; 135(1):14–16.
5. Dubernard JM, Owen E, Herzberg G, et al. Human hand allograft: report on first six months. Lancet 1999; 353:1315–1320.
6. Jones JW, Gruber SA, Barker JH, Breidenbach WC. Successful hand transplantation. One-year follow-up. Louisville Hand Transplant Team. N Engl J Med 2000; 343:468–473.
7. Siegler M. Ethical issues in innovative surgery: should we attempt a cadaveric hand transplantation in a human subject? Transplant Proc 1998; 30:2779–2782.
8. Malt RA, McKhann CF. Replantation of severed arms. JAMA 1964; 189:716–722.
9. Chen CW, Chien YC, Pao YS. Salvage of the forearm following complete traumatic amputation; report of a case. Chin Med J 1963; 82:632.

10. Zhong-Wei C, Meyer VE, Kleinert HE, Beasley RW. Present indications and contraindications for replantation as reflected by long-term functional results. Orthop Clin North Am 1981; 12(4):849–870.
11. Lee WP, Mathes DW. Hand transplantation: pertinent data and future outlook. J Hand Surg [Am] 1999; 24(5):906–913.
12. Meyer VE. Hand amputations proximal but close to the wrist joint: prime candidates for reattachment (long-term results). J Hand Surg [Am] 1985; 10(6 Pt 2):989-991.
13. Tamai S. Twenty years' experience of limb replantation — review of 293 upper extremity replants. J Hand Surg [Am] 1982; 7(6):549–556.
14. Tark KC, Kim YW, Lee YH, Lew JD. Replantation and revascularization of hands: clinical analysis and functional results of 261 cases. J Hand Surg [Am] 1989; 14(1):17–27.
15. Jones TR, Humphrey PA, Brennan DC. Transplantation of vascularized allogeneic skeletal muscle for scalp reconstruction in a renal transplant patient. Transplant Proc 1998; 30:2746–2753.
16. Guimberteau JC, Baudet J, Panconi B, et al. Human transplant of a digital flexion system vascularized on the ulnar pedicle: a preliminary report and 1-year follow-up of two cases. Plast Reconstr Surg 1992; 89:1137–1147.
17. Hofmann GO, Kirschner MH, Wagner FD, et al. Allogeneic vascularized transplantation of human femoral diaphyses and total knee joint: first clinical experiences. Transplant Proc 1998; 30:2754–2761.
18. Strome M, Stein J, Esclamado R, et al. Laryngeal transplantation and 40-month follow-up. N Engl J Med 2001; 344(22):1676–1679.
19. Lee WP, Yaremchuk MJ, Pan YC, et al. Relative antigenicity of components of a vascularized limb allograft. Plast Reconstr Surg 1991; 87(3):401–411.
20. Min Z, Jones NF. Limb transplantation in rats: immunosuppression with FK-506. J Hand Surg [Am] 1995: 20:77–87.
21. Fealy MJ, Umansly WS, Bickel KD, et al. Efficacy of rapamycin and FK-506 in prolonging rat hind limb allograft survival. Ann Surg 1994; 219:88–93.
22. Benhaim P, Anthony JP, Lin LY, et al. A long-term study of allogenic rat hindlimb transplants immunosuppressed with RS-61443. Transplantation 1993; 56(4):911–917.
23. Benhaim P, Anthony JP, Ferreira L, et al. Use of combination of low-dose cyclosporine and RS-61443 in a model of composite tissue allotransplantation. Transplantation 1996; 61(4):527–532.
24. Lance EM, Inglis AE, Figarola F, Veith FJ. Transplantation of the canine hind limb. Surgical technique and methods of immunosuppression for allotransplantation. A preliminary report. J Bone Joint Surg Am 1971; 53:1137–1149.
25. Goldwyn RM, Beach PM, Feldman D, Wilson RE. Canine limb homotransplantation. Plast Reconstr Surg 1966; 37:184–195.
26. Daniel RK, Egerszegi EP, Samulack DD, et al. Tissue transplants in primates for upper extremity reconstruction: a preliminary report. J Hand Surg [Am] 1986; 11:1–8.
27. Stark GB, Swartz WN, Narayanan K, Moller AR. Hand transplantation in baboons. Transplant Proc 1987; 19:3968–3971.
28. Hovius SE, Stevens HP, van Nierop PW, et al. Allogenic transplantation of the radial side of the hand in the rhesus monkey: I. Technical aspects. Plast Reconstr Surg 1992; 89:700–709.
29. Stevens HP, Hovius SE, Heeney JL, et al. Immunologic aspects and complications of composite tissue allografting for upper extremity reconstruction: a study in the rhesus monkey. Transplant Proc 1991; 23(1 Pt 1):623–625.
30. Ustuner ET, Zdichavsky M, Ren X, et al. Long-term composite tissue allograft survival in a porcine model with cyclosporine/mycophenolate mofetil therapy. Transplantation 1998; 66:1581–1587.
31. Jones JW, Ustuner ET, Zdichavsky M, et al. Long-term survival of an extremity composite tissue allograft with FK506-mycophenolate mofetil therapy. Surgery 1999; 126:384–388.
32. Barker JH, Jones J, Breidenbach WC, editors. Proceedings of the international symposium on composite tissue allotransplantation. Transplant Proc 1998; 30:2687–2787.
33. Jones NF. Debate: concerns about human hand transplantation in the 21st century. J Hand Surg 2002; 27A:771–787.
34. Francois CG, Breidenbach WC, Maldonado C, et al. Hand transplantation: comparison and observation of the first four clinical cases. Microsurgery 2000; 20:360–371.
35. Carroll D. A quantitative test for upper extremity function. J Chron Dis 1965; 18:479–491.
36. Herndon JH. Composite-tissue transplantation — a new frontier [editorial]. N Engl J Med 2000; 343:503–505.

Uterus Transplantation

ALBERT ALTCHEK, M.D.

Abstract

Until recently, only life and death situations warranted organ transplantation. Nonvital transplantation, to further a patient's wishes and goals, was not considered justified. It can be argued, however, that this distinction is not morally significant. Patients with kidney failure, for example, can be kept alive by dialysis. But their quality of life would be greatly enhanced by kidney transplant, which is thus considered a justified procedure. So a spectrum of rationales may justify transplantation. Transplantation of the uterus would relieve the anguish of women who greatly desire to conceive a child. Some women do not have a uterus. In some cases this is due to a congenital absence (Rokitansky's syndrome). In other cases, surgical removal of the uterus was required to repair an obstetrical rupture. With a transplanted uterus, many of these women could have the opportunity to become pregnant as a result of nonvital organ transplant.

While other organ transplant donations most often come from cadavers and less often from living donors (kidney or partial liver), the donor source for a uterus may be an otherwise healthy living patient who requires uterus removal as a standard care procedure. Furthermore, it should be possible to remove the transplanted uterus from the recipient after successful pregnancies, so the patient would not be subjected to lifelong antirejection medications.

Since animal uterus transplantation has been done successfully, human uterus transplantation might be considered for select cases. One such case has been reported.

Key Words: Uterus transplantation, quality of life surgery, prolapse uterus utilization, ethics.

Introduction

PEOPLE UNFAMILIAR WITH TRANSPLANTATION tend to think of it as only a life-saving procedure. This picture of transplantation, however, is not consistent with the longstanding facts. For more than twenty-five years, kidney transplantation has significantly improved patients' quality of life, even though dialysis is a life-preserving alternative. In addition, corneal transplant is a well-accepted therapy, and it is performed only to improve a patient's quality of life, not to preserve it. For similar reasons, autotransplantation, such as reattaching severed limbs, has been recognized as an ethical procedure. In what follows, the possibility of uterine transplant will be assessed as an intervention that will significantly improve a patient's quality of life.

In the past, skepticism about nonvital transplantation procedures was justified by the high likelihood of organ rejection. But, over the past two decades, transplantation technology and immunosuppression have advanced and the prognosis of transplantation has improved. These advances make transplantation a possible new treatment option for patients who wish to improve their quality of life.

Questions Pertaining to Uterus Transplantation

The Ethics Committee of the American Society for Reproductive Medicine has never addressed the issue of uterine transplantation. Its reports have focused on the ethics of procedures that are already being performed, not on possible future procedures. Before the procedure is performed, we must consider two crucial questions. Is uterine transplantation feasible? Is it justified?

The uterus enables a woman to menstruate and become pregnant. Most would agree that merely being able to menstruate is not important enough to justify the risks associated with solid organ transplantation. But for many

---

Clinical Professor and Chief of Pediatric and Adolescent Gynecology, Department of Obstetrics, Gynecology and Reproductive Science, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Albert Altchek, M.D., 1 East 89th Street, New York, NY 10128.

Presented at the Issues in Medical Ethics 1999 Conference at the Mount Sinai School of Medicine, New York, NY on December 10, 1999. Updated as of December 31, 2002.

women, the ability to become pregnant can be very important. For them, childbearing fills a deep emotional and social need, and they may feel a corresponding sense of loss if they are unable to conceive and give birth.

It is likely that for many women the intense desire to become pregnant is, at least in part, an innate feature of evolutionary biology. But there may be a stronger social component to this desire. Historically, in many cultures, to be barren was to be cursed. Having a child, on the other hand, meant that one was blessed and honored, perpetuating a family and a name. Yet desire alone does not justify transplantation. This emotional need has to be balanced against the feasibility of transplantation and the possible risks to the woman and child.

A uterine transplant could be an appropriate treatment for women who have no uterus but whose reproductive system is otherwise normal. For some women, the absence of the uterus is a congenital problem (known as Rokitansky's syndrome, or Müllerian agenesis). Other women may not have their uterus because of a previous hysterectomy, or they may be at risk for a uterine rupture should they become pregnant (Table).

Women who have had a hysterectomy or who have a high risk of rupture, and have already been pregnant, have the advantage of having large uterine vessels, which might facilitate the vascular anastomoses of a uterine transplant and increase the chance of a vaginal delivery.

A variety of considerations will make a woman a good candidate for uterine transplantation:

- an intense desire to become pregnant
- a good understanding of the known and an appreciation of the unknown risks associated with the transplant and with postoperational long-term immunosuppression
- emotional maturity
- ability to give informed consent
- excellent general health
- age under 35 — older patients have a lower chance of achieving pregnancy and a greater chance of having complications (e.g., hypertension, diabetes and uterine fibroids) and needing cesarean section.
- no evidence of inability to be a good mother
- expectation that the patient will comply with regimens of post-transplant immunosuppression and monitoring

TABLE

Women Who Need a Uterus to Become Pregnant

1. Congenital anomalies
    a) Rokitansky syndrome (Müllerian agenesis): congenital absence of uterus and vagina
    b) rudimentary noncommunicating or nonfunctioning uterine horn
2. Previous hysterectomy for
    a) postpartum hemorrhage
    b) invasive adherent placenta accreta
    c) rupture of uterus during pregnancy
        1) difficult delivery
        2) rupture of scar of previous caesarean section
3. High risk of rupture of uterus
    a) previous pregnancy rupture and repair of classical caesarean section scar
    b) previous very extensive myomectomies or removal of extensive adenomyosis

Rokitansky's Syndrome Patients

Patients with the Mayer-Rokitansky-Küster-Hauser syndrome, or Müllerian agenesis, have congenital absence of the uterus and vagina. Their ovaries, however, are present, with normal function and ovulation. The fallopian tubes may or may not be present. About one-third of these patients also lack a kidney but have normal renal function and normal chromosomes. These patients also have normal female physical characteristics and behavior.

This syndrome is usually diagnosed between ages 15 and 17, when the patient seeks medical treatment for amenorrhea (i.e., the absence of menstruation). Theoretically, the condition should be diagnosed at birth or at well-child routine examinations. Unfortunately, many pediatricians were never trained to inspect the vulva or may avoid performing the examination due to fear of accusations of lewdness. In addition, when the question of amenorrhea is raised, pediatricians often give incorrect reassurance that the patient is maturing normally, due to evidence of increased height, breast development, the appearance of pubic and axillary hair, feminine contour, and psychological development. Furthermore, tests of hormones, ovulation and chromosomes would all provide normal results.

In my consultation practice, I am sometimes the first to examine the patient for abnormalities. Although the vulva looks normal, there is only a dimple where the opening of the vagina should be (Fig. 1). On rectal examination, the cervix and uterus cannot be palpated. These findings are sufficient for the presumptive diagnosis. The patient will never menstruate and she will never become pregnant. This information is a catalyst for an outburst of emotion and tears from both the patient and her mother. The patient questions why she is being "punished." As the diagnosis usually occurs during the teenage years, the patient's natural idealistic, optimistic outlook is virtually shattered. Suicide becomes a concern. Even the mother is unable to cope with the immediate diagnosis. She wonders if she did not rest enough or eat enough during the pregnancy. The etiology of these disorders is unknown, and very rarely is there a genetic link. The family, however, is almost always very supportive and willing to do whatever it takes to help the patient. It is standard treatment to recommend psychological or psychiatric care, as this diagnosis can be devastating. However, the patients often refuse to seek counseling. As a result, I am often forced to become their lifelong physician, as well as a practical psychiatrist and counselor.

The diagnosis does not necessarily mean that the patient will be unable to lead what most consider a normal life. A vagina can be created, usually by dissecting a space between the bladder and rectum and lining it with a split-thickness graft (McIndoe technique) from an inconspicuous area such as the buttocks. The graft comes from her own tissue, so there is no rejection. This surgery allows the patient to have a normal sex life with orgasm. Moreover, adoption is always a possibility, and the patient who wishes to have a biological child can have her eggs removed by needle aspiration, combined with her husband's sperm, and placed in another woman's uterus (*in-vitro* fertilization combined with surrogate motherhood). Yet, most patients seem eager for uterine transplantation.

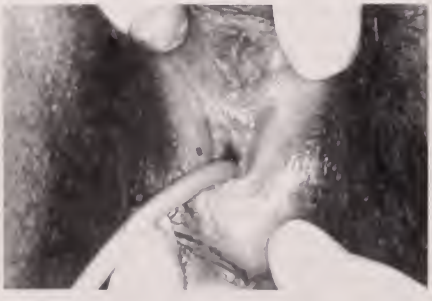

Fig. 1. The vulva in Rokitansky's syndrome is normal. However, where the vagina should be, there is simply a dimple, which in this case has a ruffled surface appearance. A Foley catheter is in the urethra anteriorly.

Patients with Rokitansky's syndrome are in otherwise excellent health and have good renal function. Therefore, if transplantation and pregnancy were to occur, it is likely that there would be no higher incidence of hypertension, preeclampsia, renal dysfunction, and premature labor than has been the usual experience during pregnancy.

However, significant problems could arise. Before a uterus is transplanted, an acceptable vagina must be created. This procedure is usually performed in young adulthood, most often during the summer vacation between high school and college. The neovagina might not be soft and pliable in labor, so the patient still might require a prophylactic caesarean section to avoid a tear. Another foreseeable problem is the congenital absence of the uterine artery and veins. This would require the anastomosis of numerous proximal branches of the internal iliac vessels. Preoperative angiography might, therefore, be helpful in preparing for transplantation.

Sources of Donor Uterus

Ideally, the donor uterus should be of normal size, usually from a donor after late puberty (approximately age 15) and presumably before arteriosclerotic changes might occur (approximately age 45). Recently, postmenopausal women have had successful pregnancies using donor eggs and hormonal preparation of the uterus. Physiologic ovarian failure, rather than uterine failure, is usually the reason that infertility occurs during menopause. Therefore, even the uterus of an "older" donor might function in pregnancy. As with other transplants, the uterus might be cadaveric or from a living donor, from either a relative or an altruistic volunteer.

There are various situations in which uterus donation would make sense. For women who do not wish to become pregnant again, a standard treatment for prolapse of the uterus is vaginal hysterectomy. A uterus that is removed in this procedure is usually normal and typically discarded. If the uterus is donated for transplant rather than discarded, the donor is placed at no additional risk. Hysterectomy is also a standard treatment option for menorrhagia (heavy menstrual periods), due to submucosal fibroid which distorts the endometrial cavity. The fibroid can be removed after the hysterectomy. In the treatment of benign ovarian neoplasms in a peri-menopausal woman, it is standard practice to remove both ovaries and confirm their pathology by frozen section. In this procedure, the uterus is sometimes removed to avoid the small chance of cancer and to avoid the need for progestin when hormonal estrogen replacement therapy is used. Thus, patients who desire no future pregnancy or who do not want to maintain menses might choose to become uterus donors.

In recent years, it has become standard practice to perform prophylactic oophorectomy, and at present salpingo-oophorectomy, usually by laparoscopy, on women with a strong familial history of ovarian cancer (in 2 or more first-degree relatives). This procedure is done at an early age after childbearing, particularly in patients with a BRCA gene abnormality. An altruistic patient might also request a simultaneous hysterectomy so that she could donate her uterus. Some institutions now do this as a routine with salpingo-oophorectomy. The donor patient would no longer require progestin as part of estrogen hormone replacement therapy and would eliminate the possibility of intramural and tubal uterine cancer. Any other condition that was considered an appropriate reason for hysterectomy could also be an occasion for uterus donation.

The altruistic donor, however, would be a woman who wishes to donate her uterus after she has concluded childbearing. A family member might be most inclined to serve as a uterus donor, and a related donor often has a closer tissue match. Mothers of Rokitansky's syndrome patients, for example, often volunteer to serve as surrogates for their daughters. They might similarly volunteer as uterus donors for transplantation.

Preparation

The Patient

Patient selection would be critical. Some patients have an overwhelming desire to have their own child, and others simply want to have a child. The latter could be satisfied by adoption. Of course adoption is not always easy to arrange, and an adopted child would not be biologically related. A biologically related child could be created by ovum aspiration, *in-vitro* fertilization and the aid of a surrogate mother. Although this could be technically simple, the involvement of a surrogate mother may introduce complicated social and legal problems related to adoption.

Thus, the appropriate patient should have a strong desire to have her own biological child, plus a willingness and physical and emotional ability to undergo the risks, pains and disabilities of the surgery and recuperation required to make pregnancy and childbirth a reality.

The patients should have extensive psychological evaluation prior to selection, and continuous emotional support after transplantation. The first transplant patients should understand that uterus transplantation has never before been performed in humans. Thus, there would be expected known risks and possible unknown risks. The former would include risks associated with anesthesia, surgery, graft rejection and antirejection medication, susceptibility to infection, and increased long-term possibilities of diabetes, hypertension, and neoplasia, as well as the risks of *in vitro* fertilization, should that be necessary. Presumably the long-term problems would be reduced by later removal of the transplanted uterus. Recipients of uterine transplants would have to be disease free, so there would be no additional expectation of long-term morbidity associated with preexisting disease.

In the process of obtaining informed consent, the physician would need to clearly explain that perfect (or even satisfactory) results cannot be guaranteed. This fact might well have to be included in the consent statement itself.

The Hospital

The institution must see to it that the patient is able to understand the entire procedure and to give informed consent. The institution must also assure the patient that it has appropriate resources for the transplant surgery and that it has an experienced multidisciplinary medical team that is well prepared to perform the procedure and to provide the necessary post-transplant care.

The Procedure

Preliminary uterus transplantation will first have to be studied in relatively large animals which approach human size, such as dogs, pigs or even primates. An appropriate animal model will have to be developed and tested in order to practice vascular anastomoses, achieve successful pregnancy and newborns, and check antirejection medication levels and doses. It might also be feasible to investigate why the uterus normally does not reject the fetus.

Prior to human recipient uterus transplantation, consideration will have to be given to arterial and venous angiography, in order to plan anastomoses sites. This would be important in Rokitansky's syndrome because of possible vascular anomalies; the critical part of this type of surgery would be the vascular anastomoses. The uterus has a unique internal circulation system that is markedly different from those of other organs. For example, while each kidney most often has a single, separate artery and vein, the uterus has a symmetrical circulation from a lateral uterine artery on each side, resulting from the embryonic fusion of the paired bilateral Müllerian duct to form a single uterus. Each uterine artery runs cephalad in a wavy fashion along the lateral border of the uterus to the cornual tubal angle, where it turns abruptly laterally through the broad ligament running under the fallopian tube, to which it sends anastomosing branches, and finally joins the ovarian (infundibulopelvic) artery, which has an additional cephalad origin from the aorta. Thus, there is a vertical anastomosing bilateral arterial supply of the uterus and ovaries. In addition, the interior of the uterus has multiple anastomosing arcuate horizontal arteries connecting each uterine artery running in both anterior and posterior walls. These circumferential arteries give off small radical branches going deep into the uterine cavity (Figs. 2 and 3) (1, 2). Furthermore, the arterioles of the uterus have extensive anastomoses with those of the adjacent vagina, which receives branches from the lateral hypogastric (internal iliac) or uterine arteries. Thus, nature has endowed the pear-sized uterus with an extraordinarily abundant arterial circulation which prepares the uterus for random placentation either in the anterior or posterior wall and permits nourishment to the fetus.

In transplantation, the vaginal anastomoses would not be available and the arterial supply would come mainly from the two uterine arteries and, to a lesser extent, from the two ovarian arteries. We know that because of the numerous arterial anastomoses, ligation of both uterine arteries for post-partum hemorrhage does not cause ischemic necrosis of the uterus. Hence, even if one uterine artery anastomosis failed, there would probably be adequate circulation from the extraordinarily extensive anastomosing arteriole bed supplied by the other uterine artery. Thus, there are four arteries of concern: two uterine and two ovarian. Assuming that there are functioning ovaries with adequate ovarian arteries, only two uterine artery anastomoses might be required, because these arteries extend to the top of the uterus and often to the fallopian tubes.

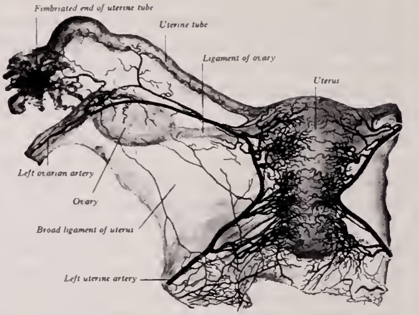

Fig. 2. In this preparation, the left uterine artery sends branches to the vagina, lateral and cornual angle of the uterus and proximal tube. It anastomoses with the left ovarian artery, which also supplies the distal tube and ovary. Reproduced with permission from: Williams PL, editor. Gray's Anatomy. 38th ed. New York: Churchill Livingstone; 1995. p. 1872. Fig. 14.27 (1).

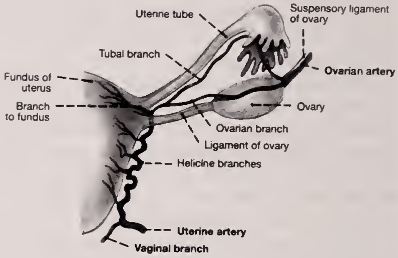

Fig. 3. Diagram of the uterine and ovarian arteries, seen in about 90% of the individuals showing the cephalad uterine artery in which a tubal and ovarian branch anastomoses with the ovarian artery. Reproduced with permission from: Sobotta. Atlas der Anatomie des Menschen. Bd 1, 21. Aufl. München: Urban & Fischer; 2000. Can also be found in Clemente CD. Anatomy: a regional atlas of the human body. 4th ed. Baltimore (MD): Lippincott Williams & Wilkins; 1997. Fig. 406 of plate 264 (2).

Arteries are thick walled and relatively easy to anastomose to feeding vessels. If the transplanted uterus comes from a cadaver, then it should be simple to transplant a segment of free uterine artery stump with the arteries. In the usual hysterectomy, the uterine arteries are cut flush with the side of the fibromuscular cervix, which makes anastomosis difficult. Using a synthetic vessel segment to create a free artery stump would not be suitable in transplantation, because it would not dilate with pregnancy. Therefore, in the living donor, the technique would have to use a modified hysterectomy procedure to excise a free uterine artery stump with the uterus. This would slightly increase the surgical time and donor risk, since it is necessary to avoid damage to the underlying ureters on each side.

The recipient feeder artery for anastomosis could be the proximal uterine artery stump or the hypogastric (internal iliac) artery. The required arterial anastomosis for the recipient uterus transplant would be the paired uterine arteries. This should be feasible, because there are only two easily identified vessels with thick walls. Even if one failed, the other should be able to provide adequate circulation.

The real problem in performing uterus transplantation is the venous circulation. Veins run with arteries but are more numerous, and they are narrower, thin walled, and delicate. They have a variable gross anatomy and do not coalesce into a large vein until much beyond their exit from the uterus. Anatomists have never paid much attention to them except to indicate an extensive, continuous, dense plexus of veins involving the uterus, parametrium, vagina, bladder, tubes and ovaries. One approach might be intraoperative vascular injection of the uterus of the donor and/or recipient *in-situ*, together with proximal compression to distend the veins for better visualization. The veins might be anastomosed to the hypogastric vein or even the inferior vena cava. Theoretically, almost any sizable anastomosed vein could drain the uterus because of the extensive venous plexuses. An operating microscope with a 300-mm objective lens might be required for deep pelvis visualization. A vascular surgeon should be involved in this part of the procedure.

Usually, there are two narrow ovarian veins and one ovarian artery on each side. The right ovarian veins drain into the vena cava. The left ovarian veins drain into the left renal vein, since the inferior vena cava is on the right side. If possible, the uterus should be transplanted with the accompanying fallopian tubes to permit the possibility of natural fertilization. An intraoperative decision would have to be made to check the circulation of the tubes. If necessary, an ovarian artery anastomosis to a tubal artery might be required.

Care would also be required to prevent adhesions to the surface of the ovary by using oxidized cellulose covering. The normal uterus is held in place mainly by the cardinal ligaments on each side of the cervix, which extend around the uterine vessels and the sacrouterine ligaments. These "ligaments" are simply condensations of connective tissue (endopelvic "fascia") with contained small blood vessels. The paired round ligaments of the uterus, which extend from the cornual angle to the internal inguinal ring, can be readily reconstructed.

It is not feasible to anastomose the nerves. Labor would therefore be painless, as it is in women with a severed spinal cord. The patient would have to be instructed when to push. Also, if a vagina had been made with split-thickness skin graft or if it was not pliable, a prophylactic caesarean section might be advisable, to prevent tearing of the vagina.

Experimental Transplantation

Animal Studies

There have not been many reports of animal experiments involving transplantation of the uterus. In 1964, reimplantation of the uterus and its appendages, using omentopexy for revascularization, was accomplished in sheep, resulting in several subsequent pregnancies (5). In 1966, the uterus, ovaries and tubes of dogs were removed *en bloc* and reimplanted in their original positions by reanastomosis of the hypogastric arteries and of the hypogastric or common iliac veins. The ovarian vessels were not reanastomosed. The average period of ischemia was 20 minutes. The reimplanted structures functioned normally. Of 8 dogs, 2 had successful pregnancies and a third was pregnant when the study was published. The authors concluded that "clinical uterine-ovarian homotransplantation would be feasible should the immunologic-rejection problem be solved" (6). Some duplicated these results (7, 8), while others tried an approach that used the aorta and vena cava (9). Experimental models that required the use of major vessels would be more hazardous (10).

Autotransplants of subtotal abdominal hysterectomies with bilateral salpingectomy in adult rhesus monkeys, using vascularization of an omental pedicle, have functioned successfully. However, there was no pregnancy because of tubal fibrosis and occlusion. Homotransplants were rejected (11). Nonvascularized 1 cm pieces of uterus reimplanted into the opposite horn of the uterus (autograft) of rats resulted in pregnancy (12). Pregnancy has occurred after vascularized contralateral autotransplantation of the fallopian tube in the ewe (13). In sheep, autotransplantation of frozen/thawed strips of ovarian cortex was still cyclically active for two years, although there was a drastic reduction in the total number of primordial follicles (14).

En-bloc vagino-utero-ovarian vascular transplantation between syngeneic Lewis rats was performed successfully without antirejection medication, but there were no subsequent pregnancies (15). This represents the survival of the uterus transplanted from another animal, based on the close relationship of donor and recipient. With cyclosporine antirejection therapy, the nonvascular, unilateral, homotransplanted rabbit uterus survived (16). In syngeneic rats, *en-bloc* vascularized adnexal isografts and allografts using cyclosporine resulted in pregnancies (17). In rats, the use of cyclosporine after tubal and ovarian allografts permitted successful pregnancy (18). In rabbits, microsurgical *en-bloc* vascularized tubo-ovarian allografts using cyclosporine resulted in successful pregnancies (19).

Human Experience

Some success with human autotransplantation suggests that uterus transplants may be feasible. Transposition of the fallopian tube by microsurgical severing of the mesosalpinx without damaging the longitudinal tubal vessels (20), transposition of the tube and ovary (21), and juxtaposition of the contralateral ovary and fallopian tube for a unicornuate uterine anomaly (22) resulted in pregnancies. Transplantation in the same individual of a vascularized midsegment tubal anastomosis also resulted in pregnancy (23). There has even been successful reimplantation of cryopreserved ovarian tissues after a year, in an attempt to preserve fertility during chemotherapy (24).

We also find some success with allografts. Human microsurgical vascularized fallopian tube allografts which were transplanted initially had good circulation. Without immunosuppression therapy, the allografts were later rejected (10, 25, 26).

There has been one human allograft uterine transplantation reported from Saudi Arabia. The recipient was a 26-year-old woman who 6 years previously had a hysterectomy for post-partum hemorrhage. The live donor was a 46-year-old woman with multiloculated ovarian cysts, who had a hysterectomy together with a bilateral salpingo-oophorectomy modified to preserve vascular structures. The donor uterus was placed in the orthotopic position. The uterine arteries and veins were extended using reversed segments of the great saphenous vein and then attached to the external ilial arteries and veins respectively. Oral cyclosporine A, azathioprine and prednisone were given orally to prevent rejection. There were two episodes of withdrawal bleeding with hormonal therapy. Acute vascular thrombosis occurred 99 days postoperatively with uterine infarction, and recipient hysterectomy became necessary. The tubes were viable and without rejection. The origin of the tubes, whether donor or recipient, was not identified.

The vascular accident was presumably due to inadequate uterine support and kinking of the uterine vascular grafts. Fageeh et al. suggested that the radial artery as well as the great saphenous vein be considered for the vascular pedicle (3).

In 1999, the first year following a kidney transplantation, the actual costs were estimated to be about $120,000. Hospital charges varied from $80,000 to $160,000. Immunosuppressive drugs range between $11,000 and $14,000 annually for kidney transplants. Medicare pays more than half the costs for kidney transplants; managed care organizations are another payor (4). Uterus transplantation is not life saving and is still considered to be in the research stage; thus it would not qualify. Nevertheless, for a select group, uterine transplantation is a significant quality-of-life issue.

Human Pregnancy after Allograft Transplantation (Usually Renal) with Immunosuppression

The vast majority of human solid organ transplants have been renal. The first reported pregnancy after a live-donor renal transplant from an identical twin sister was in 1958. Since then, there have been "over 7,000 pregnancies world-wide in renal transplant recipients alone" (27).

Fertility is not reduced by transplantation. After transplantation, the incidence of unplanned pregnancy is relatively high, occurring as early as 1–2 months after transplant. Improvement of renal function and general health may be related to improved fertility. Aside from spontaneous or voluntary abortion, in about 20–30% of these women, "the vast majority of remaining pregnancies result in live births . . . ." (28).

The rate of spontaneous abortion in the general population may be about 25%. The true incidence is probably much greater, since early abortions are often not diagnosed. Thus, for transplantation patients who are carefully observed, the incidence of first trimester abortions may not be increased significantly beyond that in the non-transplant population.

The complications of pregnancy following renal transplantation include prematurity and low birth weight in 50%, preeclampsia in 30%, infection in 20% and renal rejection in 10%. It may be difficult to distinguish between preeclampsia and rejection in the third trimester, so renal biopsy is sometimes needed for diagnosis at that time (28). Hypertension occurs in 20–60% of pregnant kidney transplant recipients. There is a "suggestion that the frequency of hypertension may be increased since the onset of the use of CsA [cyclosporine] for routine immunosuppression" (28). It is not clear whether the hypertension is related to the failure of the renal transplant, the immunosuppression medication or a combination of both. "The main toxicities of cyclosporine are nephrotoxicity and hypertension" (29).

For human uterine transplantation, the recipient would have to have normal kidneys and normal blood pressure. Yet we do not know if cyclosporine immunosuppression would cause hypertension or if pregnancy would cause hypertension and preeclampsia. In animal uterine transplant research with cyclosporine, there is no mention of hypertension. Either hypertension did not occur or blood pressure was not tested. Apparently, cyclosporine has no obvious adverse effects on the fetus (30).

Although the transplanted kidney is in the pelvis, it is not in the lower pelvis. At first, deliveries for transplant recipients were done by caesarean section. Today, sections are only done for obstetric indications (28). The chance of birth defects is not increased beyond the baseline of 3% and there is no particular related birth defect.

The better the prepregnancy maternal health and the better the status of the transplanted organ, the less the risk to the health of the mother, the fetus-newborn, and the transplanted organ (25). The National Transplantation Pregnancy Registry (NTPR) was established in 1991 as an ongoing database for the US, and later for Canada and Puerto Rico (30). According to their records, there were 588 recipients of kidney transplants with 896 pregnancies reported from 1991 to November 1999 (30). This group had a high incidence of maternal hypertension, diabetes during pregnancy, infection, and preeclampsia (30). The rate of spontaneous abortions, 13–27% (30), was somewhat lower than that of the general population. The live birth rate of 75% (30) is an extraordinarily good result. The summary indicated that the "majority of kidney recipients appear to tolerate pregnancy well, a small percentage develops (renal) rejection, graft rejection and/or graft deterioration."

There were 947 pregnancies and 972 births (including multiple pregnancies) in the 619 recipients of kidney transplants for the interval 1991 to November 2000. The results were similar to the previous report. For those patients using cyclosporine A to prevent rejection, 63% had hypertension, 12% had diabetes, 22% had infection and 30% had pre-eclampsia. Spontaneous abortion occurred in 12%, live births in 75%, and prematurity in 52%. Within 2 years of delivery, 7% had renal graft loss (27).

Conclusion

It is feasible to consider transplanting a human uterus and achieving a successful pregnancy using allograft organs, vascular anastomoses and antirejection medication.

The transplanted uterus could be cadaveric or come from a living donor. After a successful pregnancy, the uterus could be removed and the antirejection medication discontinued.

An intense desire for pregnancy by a woman who lacks a uterus might justify uterus transplantation. Any institution that chooses to undertake such a program would have to select the patients very carefully. They would also have to assemble an experienced institutional team and have adequate resources for continuous patient care. The procedure would be expensive.

If transplantation of the uterus is undertaken, it must be performed with extraordinary monitoring and in the context of research protocol. Such a study might shed light on the enigma of why the uterus does not reject foreign fetal tissue or tumors.

References

1. Williams PL, editor. Gray's anatomy. 38th ed. New York: Churchill Livingstone; 1995. p. 1872. Fig. 14.27.
2. Clemente CD. Anatomy: a regional atlas of the human body. 4th ed. Baltimore (MD): Williams & Wilkins; 1997. Fig. 406 of plate 264.
3. Fageeh W, Raffa H, Jabbad H, Marzouki A. Transplantation of the human uterus. Int J Gynaecol Obstet 2002; 76:145–251.
4. Steinman TI. Economics of transplantation. In: Norman DJ, Turka LA, editors. Primer on transplantation. Mount Laurel (NJ): American Society of Transplantation; 2001. pp. 192–197.
5. Zhordania JF, Gotsiridze OF. Vital activity of the excised uterus and its appendages after their autotransplantation into omentum. Acta Clin Plast 1964; 6:23–32.

6. Eraslan S, Hamernik RJ, Hardy JD. Replantation of uterus and ovaries in dogs, with successful pregnancy. Arch Surg 1966; 92:9–12.
7. Chiapponi PL, Delort P, Hermab Essiere J, et al. Autotransplantations totales de l'uterus chez la chienne. J Chir (Paris) 1971; 101:279–292.
8. Paldi E, Gal D, Barzilai A, et al. Genital organs. Auto and homotransplantation in forty dogs. Int J Fertil 1975; 20:5–12.
9. Truta E, Popa IP, Ionescu M, et al. [Experimental transplantations of internal genital organs] [French]. Bull Soc Int Chir 1969; 28:153–157.
10. Cohen BM. Fallopian tube transplantation and its future. Clin Obstet Gynecol 1980; 23:1275–1292.
11. Scott JR, Pitkin RM, Yannone ME. Transplantation of the primate uterus. Surg Gynecol Obstet 1971; 133:414–418.
12. La Sala G, Antoine JM, Salat-Baroux J, Roland J. [Free uterine autograft fragments interposed on the opposite uterine horn in the female rat] [French]. J Gynecol Obstet Biol Reprod (Paris) 1985; 14:39–42.
13. Cohen BM, Morgenthal JC, Davey DA, et al. Completed pregnancy following vascularized heterotopic autotransplantation of the fallopian tube in the ewe. Int J Fertil 1976; 21:153–158.
14. Baird DT, Webb R, Campbell BK, et al. Long-term ovarian function in sheep after ovariectomy and transplantation of autografts stored at -196 C. Endocrinology 1999; 140:462–471.
15. Lee S, Mao L, Wang Y, et al. Transplantation of reproductive organs. Microsurgery 1995; 16:191–198.
16. Confino E, Vermesh M, Thomas W Jr, Gleicher N. Non-vascular transplantation of the rabbit uterus. Int J Gynaecol Obstet 1986; 24:321–325.
17. Scott JR, Hendrickson M, Lash S, Shelby J. Pregnancy after tubo-ovarian transplantation. Obstet Gynecol 1987; 70:229–234.
18. Cornier E, Sibella P, Chatelet F. [Histological studies and functional results of tubal and ovarian transplants in the rat (isografts and allografts treated with cyclosporin A)] [French]. J Gynecol Obstet Biol Reprod (Paris) 1985; 14:567–573.
19. Carmona F, Balasch J, Gonzalez-Merlo J. Ovarian function, tubal viability and pregnancy after tubo-ovarian transplantation in the rabbit. Hum Reprod 1993; 8:929–931.
20. Volk M, Obermaier W, Tabatabai K, et al. [Transposition of the fallopian tube as a therapeutic possibility in special cases of tubal sterility] [German]. Geburtshilfe Frauenheilkd (Germany) 1994; 54:515–518.
21. Gamerre M, Boubli L, Colombo JC, et al. [Transposition of a tube and transposition of an ovary in the treatment of sterility] [French]. J Gynecol Obstet Biol Reprod (Paris) 1986; 15:665–669.
22. Kennard EA, Karnitis JV, Friedman CI. Juxtaposition of contralateral ovary and fallopian tube to allow pregnancy in unicornuate uterine anomaly. Am J Obstet Gynecol 1994; 171:1387–1389.
23. De Cherney A, Naftolin F. Homotransplantation of the human fallopian tube: report of a successful case and description of a technique. Fertil Steril 1980; 34:14–16.
24. Dobson R. Ovarian transplant raises hope for women facing cancer treatment. BMJ 1999; 319:871.
25. Cohen BM. Preliminary experience with vascularized fallopian tube transplants in the human female. Int J Fertil 1976; 21:147–152.
26. Wood C, Downing B, McKenzie I, et al. Microvascular transplantation of the human fallopian tube. Fertil Steril 1978; 29:607–613.
27. Armenti VT, Wilson GA, Radomski JS, et al. Report from the National Transplantation Pregnancy Registry (NT PR): outcome of pregnancy after transplantation. In: Cecka JM, Terasaki PI, editors. Clinical transplantation. Los Angeles (CA): UCLA Immungenics Center; 2000. pp. 123–130.
28. Lederer ED. Pregnancy and transplantation. In: Norman DJ, Suki WN, editors. Primer on transplantation. Thorofare (NJ): American Society of Transplant Physicians; 1998. pp. 155–162.
29. Armenti VT, Moritz MJ, Davison JM. Drug safety issues in pregnancy following transplantation and immunosuppression: effects and outcomes. Drug Saf 1998; 19:219–232.
30. Armenti VT, Wilson GA, Radomski JS, et al. Report from the national transplantation registry (NTPR): outcomes of pregnancy after transplantation. In: Cecka JM, Teraski PI, editors. Clinical transplants. Los Angeles: UCLA Immunogenetics Center; 1999. pp. 111–119.

Laryngeal and Tracheal Transplantation:

Ethical Limitations

Eric M. Genden, M.D., and Mark L. Urken, M.D.

Abstract

Over the last decade, there have been extraordinary developments in the field of transplantation science. As a result, organ transplantation enjoys a success that is unparalleled since its introduction nearly 50 years ago. Progress in the laboratory has translated into less toxic, more effective immunosuppressive therapies that have improved both allograft survival and patient quality of life. Consequently, physicians and their patients look toward a new frontier, the transplantation of non-vital organs. While the transplantation of non-vital organs is technically feasible, as demonstrated by the recent success of a human laryngeal transplant, a variety of ethical concerns must be confronted before tracheal and laryngeal transplantation can be offered to patients as a reconstructive option. When considering the risks and benefits of non-vital organ transplantation, one must consider the immeasurable impact of a procedure on the patient's quality of life. The focus of this article is on quality of life and the role of laryngotracheal transplantation in contemporary medicine.

Key Words: Laryngeal transplantation, surgery, ethical consideration.

"Among experiments that may be tried on man, only those that do harm are forbidden, those that are harmless are permissible, those that do good are obligatory."

—*Bernard, 1865* (1)

Since Jaboulay attempted the first kidney transplant nearly a century ago (2), there has been remarkable progress in the field of clinical organ transplantation. Over the last decade, research in transplant immunobiology and the development of new immunosuppressive agents have made organ transplantation safer and less toxic for patients. As a result, physicians, medical ethicists, and patients look to a new frontier, the transplantation of non-vital organs.

Reconstruction of circumferential tracheal defects greater than 6.4 centimeters long or of 50% of the total tracheal length, remains a reconstructive dilemma (3). Attempts at reconstruction with prosthetic materials (4, 5), autogenous grafts (6 – 10), or fresh radiated and cold pretreated (11, 12) trachea, have been largely unsuccessful. Consequently, patients who sustain extensive cervical tracheal defects are left with a stomal airway, while significant thoracic tracheal defects are often not compatible with life.

Similarly, patients who have undergone a laryngectomy as a result of either trauma or cancer, are socially handicapped. Unable to communicate without the use of an electrolarynx or a tracheoesophageal prosthesis, patients often become socially isolated and suffer from major depression (13, 14). Patients in whom the larynx has been removed, or who have defects in their tracheal airway, must maintain a stomal airway without the benefit of a normal voice. While ischemic injury has limited the clinical application of laryngeal and tracheal transplantation, recent success with direct revascularization (15, 16) and a well-documented compromise in the quality of life of these patients (14), has led investigators to reexamine allotransplantation.

Address all correspondence to Eric M. Genden, M.D., Assistant Professor, Department of Otolaryngology-Head and Neck Surgery, Box 1189, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Presented at the Issues in Medical Ethics 1999 Conference at the Mount Sinai School of Medicine, New York, NY on December 10, 1999, and updated as of January 2002.

Transplantation of the larynx and trachea is not a new concept. In the early 1960s and 1970s several investigators attempted both laryngeal (17, 18) and tracheal transplantation (12) in the canine model. A poor understanding of the immunobiology related to these organs as well as a limited ability to reliably revascularize these allografts resulted in marginal success. Furthermore, immunosuppressive agents available at the time were non-specific, leading to global immunosuppression and a high risk of immunosuppression-related illnesses. This raised obvious concerns regarding the safety of clinically transplanting non-vital organs into otherwise healthy patients. Technical limitations, non-selective immunosuppression, and ethical concerns regarding the transplantation of non-vital organs resulted in a 20-year investigational hiatus.

Technical Limitations

A number of developments over the last 5 years have prompted investigators to reexamine tracheal and laryngeal transplantation. In particular, our group has made great strides in resolving several of the technical issues related to revascularizing long segment tracheal allografts. Recent work in the laboratory has defined the vascular territory of the cranial thyroid artery (19) and, for the first time, has enabled our team to successfully transplant 12 centimeter segments of trachea based on a single vascular pedicle (16). Furthermore, Gannon et al. have defined the "peritracheal fold," a fold of investing tracheal fascia essential to successful tracheal revascularization (20). These findings have served as the basis for similar anatomical studies in non-human primates, demonstrating the feasibility of human tracheal revascularization (15).

Immunosuppression

In an effort to better understand tracheal and laryngeal allograft rejection, the antigenicity of the trachea has been characterized, demonstrating that the trachea appears to be susceptible to rejection much like other tissues (21, 22). Immunohistochemmical characterization and histological analysis by our group and others (21, 23) demonstrate that the mucosa is the major antigenic structure and is the target of allograft rejection. While the mucosa is primarily responsible for the immunogenic properties of allogenic tracheal transplants (24), immunohistochemical analysis demonstrates that the cartilage structure is only mildly immunogenic (21).

This information has been useful in targeting allograft immunosuppression. More recently, we have reported the induction of nontoxic donor-specific tolerance to rat tracheal allografts using modified donor antigen (25). This technique has enabled us to achieve complete mitigation of the T-cell-mediated rejection response, thereby preventing tracheal transplant rejection in the rat model. Currently, we are working to define mechanisms of donor-specific immunosuppression that may be applied to clinical transplantation.

Ethical Considerations

Concomitant with advances in transplantation science, there has been a focus on quality of life as it relates to medical therapy. Concern for the patient's psychological well-being has forced the medical community to look more closely at not only the potential goal of a particular therapy, but also the psychological impact of that therapy on a patient's quality of life. While just a decade ago, *survival* was considered a therapeutic endpoint, today we must also consider the impact of therapy on a patient's *quality of life*.

Concern with quality of life is particularly germane to the head and neck cancer patient because of the well-recognized stressors that have been associated with the treatment of this disease (14). Laryngeal cancer is associated with an increased risk of suicide, psychosocial stress, and a negative impact on the patient's quality of life (14, 26). As alluded to earlier, the reliance upon a permanent stoma for breathing and the impaired ability to communicate, have devastating effects on self-image and identity (14). Breitbart and Holland proposed two areas of impairment associated with head and neck cancer, disfigurement and dysfunction (26). While it is beyond the scope of this article to address the former concern, laryngotracheal transplantation may certainly address the latter impairment.

Preferences regarding treatment and reconstruction are becoming more important to patients. The impact of losing one's voice or relying upon a permanent stoma should not be underestimated (27). Evidence exists that if given the opportunity, patients would prefer to trade increased survival, to retain the normal form and function of the larynx (28). This demonstrates the central role that quality of life may play in the decision-making process. It is no longer enough to survive; patients want to enjoy their quality of survival.

Transplantation of non-vital tissues, such as the larynx and trachea, has been a point of contention since the introduction of clinical transplantation in the mid-1950s. Ethical concerns regarding the risk of transplanting non-vital tissues have prevented aggressive research in this area. Advances in transplantation science, however, have resulted in a decreased morbidity associated with clinical organ transplantation.

As patients enjoy prolonged survival as a result of advances in surgical and medical therapy, functional status, self-image, and quality of life become increasingly important. As a result, it may be more appropriate to define organs considered for transplantation, not as "vital" and "non-vital," but as "essential" and "non-essential." A functional voice and an oral airway are not *vital* to preserve life; however, mounting evidence suggests that they are *essential* to achieving an acceptable quality of life.

References

1. Bernard C. An introduction to the study of experimental medicine. 1865. Translation by Henry Greene. In: Reiser JS, Dyck AJ, Curran WJ, editors. Ethics in medicine. historical perspectives and contemporary concerns. Cambridge (MA): MIT Press; 1977. pp. 257–259.
2. Jaboulay M. La transplantation. Lyon Med 1906; 107:575.
3. Grillo HC. Circumferential resection and reconstruction of the mediastinal and cervical trachea. Ann Surg 1965; 162(3):374–388.
4. Neville WE, Bolanowski PJ, Soltanzadeh H. Prosthetic reconstruction of the trachea and carina. J Thorac Cardiovasc Surg 1976; 72(4):525–538.
5. Leake D, Habal M, Pizzoferrato A, Vespucci A. Prosthetic replacement of large defects of the cervical trachea in dogs. Biomaterials 1985; 6(1):17–22.
6. Cohen RC, Filler RM, Konuma K, et al. A new model of tracheal stenosis and its repair with free periosteal grafts. J Thorac Cardiovasc Surg 1986; 92(2):296–304.
7. Jones RE, Morgan RF, Marcella KL, et al. Tracheal reconstruction with autogenous jejunal microsurgical transfer. Ann Thorac Surg 1986; 41(6):636–638.
8. Papp C, McCraw JB, Arnold PG. Experimental reconstruction of the trachea with autogenous materials. J Thorac Cardiovasc Surg 1985; 90(1):13–20.
9. Kato R, Onuki AS, Watanabe M, et al. Tracheal reconstruction by esophageal interposition: an experimental study [see comments]. Ann Thorac Surg 1990; 49(6):951–954.
10. Letang E, Sanchez-Lloret J, Gimferrer JM, et al. Experimental reconstruction of the canine trachea with a free revascularized small bowel graft [see comments]. Ann Thorac Surg 1990; 49(6):955–958.
11. Lenot B, Macchiarini P, Dulmet E, et al. Tracheal allograft replacement. an unsuccessful method. Eur J Cardiothorac Surg 1993; 7(12):648–652.
12. Alonso WA, Bridger GP, Bordley JE. Tracheal transplantation in dogs. Laryngoscope 1972; 82(2):204–209.
13. Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients. JAMA 1983; 249(6):751–757.
14. McQuellon RP, Hurt GJ. The psychosocial impact of the diagnosis and treatment of laryngeal cancer. Otolaryngol Clin North Am 1997; 30(2):231–241.
15. Pearl AW, Gannon PJ, Urken ML. Anatomy and vascular perfusion territories of the superior thyroid artery in Macaca mulatta. Laryngoscope 1998; 108(7):1062–1065.
16. Salmeron J, Gannon PJ, Blackwell KE, et al. Tracheal transplantation: superior and inferior thyroid artery perfusion territory. Laryngoscope 1998; 108(6):849–853.
17. Silver CE, Rosen RG, Dardik I, et al. Transplantation of the canine larynx. Ann Surg 1970; 172(1):142–150.
18. Yagi M, Ogura JH, Kawasaki M, Takenouchi S. Physiological studies of the replanted canine larynx. Ann Otol Rhinol Laryngol 1966; 75(3):849–864.
19. Shaari CM, Gannon PJ, Salmeron J, et al. Tracheal transplantation: defining the vascular territory of the canine cranial thyroid artery. Otolaryngol Head Neck Surg 1999; 120(2):180–183.
20. Gannon PJ, Costantino PD, Lueg EA, et al. Use of the peritracheal fold in the dog tracheal transplantation model. Arch Otolaryngol Head Neck Surg 1999; 125(9):959–963.
21. Beigel A, Steffens-Knutzen R, Muller B, et al. Tracheal transplantation. III. Demonstration of transplantation antigens on the tracheal mucosa of inbred rat strains. Arch Otorhinolaryngol 1984; 241(1):1–8.
22. Beigel A, Muller-Ruchholtz W. Tracheal transplantation. II. Influence of genetic difference and degree of sensitization on reactions to the tracheal transplant. Arch Otorhinolaryngol 1984; 240(3):217–225.
23. Lee AG, Wagner FM, Giaid A, et al. Immunohistochemical characterization of inflammatory and proliferative events during chronic rejection in rat lung allografts. Transplantation 1997; 64(3):465–471.
24. Bujia J, Wilmes E, Hammer C, Kastenbauer E. Tracheal transplantation: demonstration of HLA class II subregion gene products on human trachea. Acta Otolaryngol 1990; 110(1–2):149–154.
25. Genden EM, Mackinnon SE, Yu S, et al. Portal venous ultraviolet B-irradiated donor alloantigen prevents rejection in circumferential rat tracheal allografts. Otolaryngol Head Neck Surg 2001; 124(5):481–488.
26. Breitbart W, Holland J. Psychosocial aspects of head and neck cancer. Semin Oncol 1988; 15(1):61–69.
27. Ackerstaff AH, Hilgers FJ, Aaronson NK, Balm AJ. Communication, functional disorders and lifestyle changes after total laryngectomy. Clin Otolaryngol 1994; 19(4):295–300.
28. McNeil BJ, Weichselbaum R, Pauker SG. Speech and survival: tradeoffs between quality and quantity of life in laryngeal cancer. N Engl J Med 1981; 305(17):982–987.

Stem Cell Transplantation

STEVEN FRUCHTMAN, M.D.

Abstract

Historically, a variety of hematological disorders of the bone marrow, such as acute leukemia, chronic myelocytic leukemia and severe aplastic anemia, were invariably fatal. In the past two decades, basic and clinical scientists have been able to change this grim reality into a more hopeful outcome by replacing the diseased bone marrow with stem cells from either a family donor or an unrelated volunteer donor with identical human leukocyte antigens (HLA). Because of progress in this field, the initial experience of mainly using sibling donors has now been expanded to the use of either unrelated adult donors or cord blood cells as a source of hematopoietic cells. These approaches have created ethical concerns for donors and families, concerns that need to be discussed and understood by patients, volunteer donors and health care professionals.

Key Words: Transplant, stem cell, stem cell transplant, ethics.

SURGICAL AND IMMUNOLOGICAL ADVANCES have permitted transplantation of organs, which has saved many lives. Nonetheless, the interplay between hematopoietic cells and successful organ transplantation merits further investigation. It has been suggested that solid organ tolerance may be enhanced when hematopoietic stem cells from the organ donor are transplanted as well. When these stem cells engraft, even if only for a short period of time, tolerance of the organ may be optimized. Therefore, expertise in the science of stem cells may play an integral role in our understanding of the tolerance required for successful organ transplantation.

There is no longer much ethical dispute about the role of allogeneic stem cell transplants (ASCT) for appropriate patients. Historically, there was enormous skepticism regarding the technology and whether or not it was improving outcomes for patients with marrow disorders. Hematologists and oncologists recently have had greater success in placing patients into remission with multiagent chemotherapy; in fact, up to 85% of patients with acute leukemia now enter remission. Unfortunately, these remissions are usually short lived, and most of these patients will relapse. Historically, once a diagnosis of acute leukemia is made for an adult, there is a 50% chance that the patient will relapse within a year and a half (1). Although childhood acute lymphocytic leukemia is cured 80–85% of the time using chemotherapy (2), the prognosis for adult patients is not as favorable. For an adult patient, once leukemia returns as either acute myelogenous leukemia (AML) or acute lymphocytic leukemia (ALL), fatality is inevitable. Thus, ASCT plays a crucial role in the treatment of adult leukemia patients.

In the United States, allogeneic stem cell transplants have been performed for treatment of two major diseases, acute leukemia and chronic myelocytic leukemia (CML). CML is characterized by a high white cell count and the presence in the marrow of a specific molecular or cytogenetic abnormality, referred to as the breakpoint cluster region / Abelson oncogene (BCR/ABL) translocation or the Philadelphia chromosome (first described in that city), respectively. While the use of the word "chronic" was chosen to differentiate this disease from acute leukemia, historically in the pre-imatinib (Gleevec) era, 50% of patients with CML died within 3–4 years of diagnosis (3). Thus, as the fatal prognosis in this time frame reveals, this disease is far from chronic. Prior to multi-agent chemotherapy, patients with acute leukemia

---

Address correspondence to Steven Fruchtman, M.D., Clinical Associate Professor of Medicine, Hematology, Box 1410, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Presented at the Issues in Medical Ethics 1999 Conference at the Mount Sinai School of Medicine, New York, NY on December 10, 1999, and updated as of December 30, 2002.

would die within three months of diagnosis, and patients who survived longer than three years were considered to be "chronic" in comparison. But in an era characterized by remarkable medical advancements, a mere three-year survival rate is not long enough to be called chronic. The 50% fatality rate associated with CML is a result of the transformation of chronic myeloid leukemia to a more acute blastic phase. Once this transformation occurs, neither chemotherapy nor ASCT is effective, and the patient generally succumbs to the underlying malignant process.

Typically, hematopoietic stem cells to be used for transplant are collected from a donor whose human leukocyte antigens (HLA) are identical to those of the recipient. The HLA system is inherited on chromosome 6, and ideally the donor should be an HLA-identical, healthy sibling, and the recipient a patient with some form of malignant marrow disease or an acquired marrow failure syndrome. Historically, bone marrow was typically collected from the posterior iliac crests. But with new technology, it is no longer necessary to collect these stem cells from the bone marrow cavity. Alternatively, these cells can be collected from the peripheral blood. However, using either approach to collect hematopoietic progenitors, there are ethical considerations. A "peripheral blood" donor must receive a granulocyte colony-stimulating factor (GCSF). There are currently no recognized long-term risks in using this agent which (a) differentiates progenitor cells along the pathway of white blood cell production and (b) releases these cells into the peripheral blood. Unfortunately, with administration of GCSF, some recipients develop fever, bone pain and a profound leukocytosis. Subjecting donors to these side effects must be considered, although it may be less of an issue for a concerned sibling than for an unrelated individual. Donated marrow, from an unrelated volunteer donor or a sibling donor, has to be collected in an operating room, and the donor must be subjected to general or epidural anesthesia and multiple aspirations of the posterior iliac crests, to harvest a sufficient quantity of bone marrow cells. Although extremely rare, there have been deaths from complications associated with general anesthesia during this procedure. For donors receiving epidural or spinal anesthesia, anesthetic complications that may be seen are headaches and epidural leaks. Other complications include local or systemic bacterial infection originating at the collection site, sciatic nerve damage from the collection needle inadvertently hitting the nerve, and bruising. Pain, typically managed by acetaminophen, is of course common. Thus, although unrelated volunteer stem cell donors are recognized as being good citizens, ethical justification for their donation must be considered because of the risks involved.

Of the first 100 ASCT patients to receive transplants at the Fred Hutchinson Cancer Research Center (Seattle, Washington), 90 died and 10 were long-term disease-free survivors. In 1990, the Nobel Prize in Medicine and Physiology was awarded to Dr. E. Donnall Thomas for this work. The question arises, if 90% of the patients went on to die with ASCT, why was he honored with such a prestigious award? Clearly, the answer resides in the subsequent technical and clinical improvements that now permit far greater numbers of patients to be cured using this approach. Moreover, these pioneering studies initiated research aimed at elucidating immunologic aspects of cancer eradication. Recently, patients who underwent ASCT for AML with an HLA-identical donor have had more successful results; in fact, 50–60% of these patients have been cured (4). However, transplants from unrelated, normal volunteer donors are less successful, because of genotypic HLA differences. Unfortunately, with the shrinking size of American families and divorce being more common, it is very difficult to identify healthy HLA-identical sibling donors for patients with acute or chronic leukemia. Thus, more often, unrelated transplants are being performed.

ASCT is also making it possible to treat pre-leukemic diseases, such as myelodysplastic syndrome, preventing the inevitable progression to fatal acute leukemia. As a result, 40% of these patients can be cured. Similarly, it is now possible to cure almost 80% of younger patients with severe aplastic anemia, if an HLA-identical sibling donor exists (5).

Unfortunately, it is not always possible to find an HLA-identical donor. Thus, other approaches, such as autologous (self) transplants and mismatched allogeneic transplants, are increasing in frequency for hematological malignancies, and umbilical cord transplants are being investigated. Younger patients have more successful outcomes after allogeneic transplants, because they have less organ toxicity and a lower incidence of graft versus host disease (6). In the past, patients older than 40 years of age were considered to be high risk, but in the era of "reduced intensity" preparative regimens, patients as old as 70 years of age are undergoing ASCT with promising results.

Of interest, the most common type of "transplant" is normal pregnancy. Not infrequently, the transplant is rejected, resulting in a spontaneous miscarriage. If the transplant is successful and tolerance of mother for the fetus is established, a newborn is delivered. Very little is known about the tolerance of the HLA-mismatched tissue, i.e., the fetus, which permits the pregnancy to be carried to term. Cord blood contains high numbers of hematopoietic progenitor cells that can completely engraft onto both a child and, with greater delay, an adult. The presence of these cells may influence the mother's tolerance for the fetus, a foreign tissue. Greater understanding about the process of tolerance during pregnancy will increase our understanding of issues of tolerance for both hematopoietic and solid organ transplantation.

Because of the difficulty in identifying an HLA-identical sibling donor for many patients, in the early 1970s the National Marrow Donor Program (NMDP) was created. The purpose of the NMDP was to create a registry of volunteer donors who have had preliminary HLA typing performed. The Department of Defense (DOD) initially funded the NMDP, because of the DOD's concern regarding the effects that nuclear war or a nuclear accident could have on the U.S. population. Most people exposed to a nuclear catastrophe die of skin burns, but the second most common cause of death due to nuclear exposure is bone marrow failure. In an attempt to develop mechanisms for rescuing such individuals exposed to lethal doses of radiation, the DOD funded the NMDP to HLA type normal volunteers, using only a specimen of peripheral blood and a computer registry maintained in Minneapolis, Minnesota. Thus, in the event of a nuclear catastrophe, potential HLA-identical volunteers could be rapidly identified and serve as stem cell donors for those exposed to a nuclear holocaust. This registry now also allows access to a list of possible HLA-identical unrelated donors for leukemia patients and others who require transplantation. Fifty percent of the ASCTs done at The Mount Sinai Hospital use donor sources from the NMDP. However, at Mount Sinai we continue to be troubled by our frequent inability to identify HLA-identical donors, even from the NMDP for our patients. Almost four million people have been HLA typed, but most are Midwestern Caucasians. Therefore, finding a match for people of African-American, Asian and Hispanic descent, the ethnic background of many of our patients, is very difficult. Thus, it is extremely important to establish umbilical-cord-blood collection procedures, as a bank of such cells would permit HLA matching for HLA types more frequently found in an institution's catchment area, i.e., types more reflective of the genetic diversity and background of the local geographical area.

It is possible to regenerate bone marrow function from cord blood, and thus cord blood can be used as a source of hematopoietic cells for patients requiring ASCT. Cord blood has many advantages. It is a virtually unlimited resource which, while once considered a useless byproduct of pregnancy, can now be used in transplantation. Even though a potential HLA-identical donor is found in the NMDP for a patient, there is a 30% chance that the potential donor will not be available at the time the bone marrow donor request is made. Many people move and neglect to give their new addresses to the NMPD and thus cannot be found. They may develop medical problems which preclude bone marrow donation. Or they may just change their minds and decide not to donate, which of course they are entitled to do. These problems do not occur with cord blood. Cord blood is immediately available, there is no donor risk, and graft versus host disease following cord blood transplantation may be lower, because the immune cells in cord blood are more immune naive than those from an adult bone marrow donor (7). Thus, HLA matching may be less relevant, because one may be able to cross genetic barriers to transplantation.

In addition to malignant marrow diseases, genetic disorders of the marrow can also be cured with ASCTs. Thalassemia, an inherited disease involving red cells and hemoglobin production, is mostly seen in people of Mediterranean descent. Transplant strategies have been studied in Italy, where pioneering work has been done in an effort to cure patients of this transfusion-dependent hemoglobinopathy (8). We have done a small number of ASCTs for this disorder at Mount Sinai. While we do not see many patients with thalassemia, we do see many patients with sickle cell disease (SCD). Can we cure patients with SCD using an allogeneic stem cell approach? The first patient who underwent an ASCT for SCD had almost 100% hemoglobin S prior to the transplant; the donor was his HLA-identical sibling with sickle trait, which is a benign situation. After transplant, the recipient exhibited a hemoglobin A level (the normal hemoglobin) of 60% and hemoglobin S level of about 40%. Thus, the recipient was converted to sickle trait, the genotype of his stem cell donor. However, the transplant was actually not done for SCD, since this recipient also happened to have developed acute lymphocytic leukemia. So both diseases, acute leukemia and SCD, were cured using an HLA-identical sibling donor.

In a national study, 22 patients with SCD underwent ASCT solely for SCD. Ten to fifteen percent of these patients succumbed and died as a complication of the ASCT (9). The question of whether this procedure carries a risk considered to be acceptable may depend on the family experience. That is, if a family has already lost a child from a complication of SCD, they may be willing to accept the risk of peritransplant mortality for the hope of a cure. But this decision is a very difficult one. In addition to the difficulty in finding an HLA match, for reasons already mentioned, an HLA-identical sibling may also have SCD, and thus cannot be a donor. This limits the number of potential family donors who could be used to cure SCD. The use of cord blood as the donor source may increase the possibility of finding HLA-identical donors for patients with SCD.

To obtain the cord blood, following normal delivery the obstetrician places a clamp across the umbilical cord, cannulates the umbilical vein and typically drains about 100–150 cc of cord blood. The cord is HLA typed, a complete infectious disease screen is performed, and the cord is placed into a freezing apparatus for long-term storage. If a patient who requires transplant is found to be HLA identical to a cord in the bank, the cord is released to the transplant center. Following an appropriate preparative regimen, the cord is thawed at the bedside and infused into an intravascular catheter in the recipient, and the cord cells migrate to sites of potential hematopoiesis in the recipient. Suppose, for example, a male patient is undergoing a cord blood transplant from a female cord donor, or vice versa. It is easy to follow these cells as the bone marrow recovers. For example, when the male recipient's white count returns to normal after using cord cells from a female donor, his marrow and peripheral blood nucleated cells will all be of the female type if the transplant is successful. Thus, successful cord blood banks will increase the number of such transplants by offering a large inventory of HLA-typed cells.

Historically, there has been much discussion about the proper way to obtain informed consent from the mother, and who owns these cells. Clearly, obtaining informed consent is not appropriate at the time of labor and delivery. The discussion regarding donating cord blood and placing it into storage for potential use for patients requiring ASCT must occur in a setting where details of the procedure can be answered, along with a description of how it can help others. If the cord blood is not released to another individual with marrow disease as a Good Samaritan effort, it will be available to the child. There are also quality assurance concerns about ensuring that the umbilical cord blood is collected in an appropriate manner. The cord and placenta are delivered through the vagina. Thus, sterility and purity of the cord cells are important, and every effort must be made to minimize potential risks associated with any contamination. This can be done by using the expertise of an obstetrician, or nursing personnel, with training in the proper technique to harvest cord cells.

Conclusion

ASCT, i.e., the use of hematopoietic progenitor cells from a related or unrelated HLA-identical person, permits the cure of malignant diseases of the marrow that historically were considered incurable. In addition, it is now being investigated in benign conditions such as sickle cell disease, where patients have serious disabilities and medical therapies have limited impact on outcomes. Newer sources of hematopoietic progenitors, such as cord blood, have helped those who would otherwise lack an appropriate donor. Most recently, by employing newer immunosuppressive approaches that are less toxic, older patients have been able to receive ASCTs. In the next decade, we need to understand mechanisms of both graft rejection and graft-versus-host disease to permit broader application of this technology for our patients and to minimize risks for both donors and recipients.

References

1. Mainwaring MG, Rimsza LM, Chen SF, et al. Treatment of refractory acute leukemia with timed sequential chemotherapy using topotecan followed by etoposide + mitoxantrone (T-EM) and correlation with topoisomerase II levels. Leuk Lymphoma 2002; 43(5):989–999.
2. Marco F, Bureo E, Bermudez A, et al. Treatment of acute leukemia in children: recent advances and future challenges. Expert Rev Anticancer Ther 2001; 1(3):479–486.
3. Barbany G. Hoglund M, Simonsson B. Complete molecular remission in chronic myelogenous leukemia after imatinib therapy. N Engl J Med 2002; 347(7):539–540.

4. Bicigalupo A, Lamparelli T, Gualandi F, et al. Increased risk of leukemia relapse with high dose cyclosporine after allogeneic marrow transplantation for acute leukemia: 10 year follow-up of a randomized study. Blood 2001; 98(10):3174–3175.
5. Kojima S, Matsuyama T, Kato S, et al. Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: The Japan Marrow Donor Program. Blood 2002; 100(3):799–803.
6. Peranteau WH, Hayashi S, Hsieh M, et al. High-level allogeneic chimerism achieved by prenatal tolerance induction and postnatal nonmyeloablative bone marrow transplantation. Blood 2002; 100(6):2225–2234.
7. 0hnuma K. Isoyama K, Nishihira H. Cord blood transplantation from HLA-mismatched unrelated donors. Leuk Lymphoma. 2002; 43(5):1029–1034.
8. Lucarelli G, Galimberti M, Polchi P, et al. Marrow transplantation in patients with advanced thalassemia. N Engl J Med 1987; 316(17):1050–1055.
9. Walters MC, Patience M, Leisenring W, et al. Bone marrow transplantation for sickle cell disease. N Engl J Med 1996; 335(6):369–376.

Candidate Selection Criteria for Living Donor Liver Transplantation

MYRON SCHWARTZ, M.D.

Abstract

Living donor liver transplantation is a new surgical technique that challenges the assumptions of the current system for allocation of livers for transplantation. Arguments based on justice in the setting of scarcity, and the consequent need for triage, do not apply. The risk to the living donor, an order of magnitude higher than that for kidney donation, raises different ethical concerns related to autonomy, what constitutes an acceptable risk-benefit equation, and who is to decide.

Key Words: Living donor candidacy, liver transplantation, ethics.

THE DEBATE RAGES on about how donor organs for transplantation should be allocated. Given the scarcity of this resource, the U.S. has established uniform criteria that a patient must meet in order to qualify as a transplant candidate. In the development of these criteria, a conscious attempt was made to balance utility and justice. In the name of justice, the system mandates that the sickest patient on the list gets transplanted first. However, utility dictates that a patient must have a certain minimal likelihood of survival before being placed on the list in the first place. Moreover, if clinical deterioration reduces the chance for success below a certain threshold, the patient is de-listed. This system, akin to wartime triage, denies potentially lifesaving treatment to many patients who, if the necessary treatment did not require a scarce donor organ, would receive therapy as a matter of course. As an example, patients with large liver tumors that for technical reasons we cannot remove would have about a 25% chance of cure with a liver transplant; on this basis, these patients are excluded from candidacy. It is standard practice, however, to remove such tumors when it *is* technically feasible, with about the same 25% chance of success.

It has been common practice for many years to remove a kidney from a healthy donor for transplantation into a relative or a friend. Donating one of an organ pair, the donor generally does not suffer noticeable long-term harm, and the likelihood of death from kidney donation is probably about 2 in 10,000. Kidney transplants are not life-saving in an immediate sense, although evidence suggests that patients with kidney failure live longer with transplants than they do on dialysis; the key issue is quality of life, which (in the 90% of cases that are successful) is clearly improved. About 10 years ago, advances in liver surgery led to the technique of taking a small portion of the liver from a healthy adult, usually a parent, to transplant in infants and small children. This approach has been proven to be both safe and highly successful, and has virtually eliminated the problem of children dying while waiting for liver transplantation. Encouraged by this experience, in 1999 we began to extend this option to adult transplant candidates. Donor safety has been a concern. In order to provide enough liver tissue to sustain life in the recipient, an entire lobe of the liver must be removed from the donor. The liver has two lobes: the left, which makes up about 40%, and the right lobe, which makes up 60%. The liver is well-known to have a remark-

---

Address all correspondence to Myron Schwartz, M.D., Recanati/Miller Transplantation Institute, Box 1104, Mount Sinai School of Medicine, 1 East 100th Street, New York, NY 10029-6574.

Presented at the Issues in Medical Ethics 1999 Conference at the Mount Sinai School of Medicine, New York, NY on December 10, 1999, and updated as of November 2002.

able regenerative capacity, such that within one month to six weeks after removal of up to 75% of the liver, volume is restored to presurgical levels. Using left lobes it is possible to transplant a recipient the same size as or smaller than the donor; however, when the donor is smaller than the recipient, or when the recipient is very sick, a left lobe will not be enough liver to do the transplant safely, and the right lobe must be used. The cumulative world experience with living liver donation suggests that the risk to a right lobe donor is somewhere between 1 in 200 and 1 in 400. While not very great, this is an order of magnitude higher than the mortality of kidney donation, estimated at 2 in 10,000.

Our intent in pursuing the development of an adult living donor transplant program was to alleviate the donor shortage and, at least for some patients, to shorten or eliminate the waiting time for a liver. It has rapidly become evident, however, once having initiated the program, that there is no a priori basis for applying the national candidate selection criteria when considering a patient for living donor transplantation. There is no role for triage. These organs are outside the donor pool in question — the living donor (except in highly unusual circumstances) is offering his or her liver only to one designated candidate.

What, then, should be the basis for candidate selection? The dictum *primum non nocere* (first, do no harm) is drummed into us from the first day of medical school. A slight shift — to do no *net* harm — opens the door for us to take an entirely healthy person and subject him or her to the major surgery of the donor operation. The pain, disability, and risk of donation are offset by the prevention of loss of the recipient. This presumes a close relationship between the two individuals such that the recipient is in a sense a part of the donor, and loss of the recipient would be tantamount to a physical injury. It also presumes a certain likelihood of success of the procedure in preventing the recipient from dying.

The question is, how high a likelihood of success (and for how long) is high enough to justify going ahead — and who is to decide? The principle of autonomy would lead us to present the facts to the donor and recipient, and let them decide. However, these decisions are hardly made dispassionately — many people seem to abandon rationality when faced with the imminent death of a loved one, and I wonder how well prospective donors actually hear the facts that we present. The most common case we face is that of the previously mentioned patient with an advanced liver tumor. As a tumor enlarges and advances within the liver, the likelihood of it having begun to spread outside the liver (even though our tests may not reveal it) rises in a predictable way. Should we accept cases with a 25% chance of cure? 10%? Do we even have to consider cure? What if there's no chance of cure, but good quality life may be extended by a year? Six months? Should our standards be different for right lobe donation, where the donor risk may be higher, as opposed to the left lobe? What if a prospective donor has other medical problems that may raise, even slightly, the risk of donation — is this a consideration that should be factored into the equation, or should it eliminate the donor from consideration?

It is easy, in the name of autonomy, to leave the decisions to the prospective donor and recipient, but it somehow feels like an abdication. Given a high risk of death for a well-meaning but innocently naive donor, should the surgeon pay heed to his or her own assessment of the risk-benefit ratio? In the name of maintaining society's trust in the medical system — that we will always act in the best interests of our patients — should we decline cases that the average person on the street would consider inappropriate? The insurance industry — in a sense, an agent of society — is beginning to pay attention, and to deny cases with a low (but not zero) chance of success. Do other resources not so clearly in short supply (manpower, utilization of hospital resources, and money) bear consideration in this costly, labor-intensive procedure?

In 1999, I presented this dilemma to a gathering of transplant patients and their families at an American Liver Foundation meeting at which I was asked to speak. Responses ranged from, "if they hear the facts and still want to go ahead, you have no right to deny them," to the hopelessly egalitarian ideal, "if a prospective donor comes forth, you should educate him or her about the organ shortage, and the donation should go to the next person up on the waiting list."

I believe there are cases where we hide behind the national allocation system; living donation unmasks us, and makes us face up to our true feelings. Take the example of alcoholic liver disease. Who really wants to transplant alcoholics — especially unreformed ones? In the name of utility, the national system requires a six-month period of abstinence before a patient can be listed. The supposed reason is that patients who are not abstinent pre-op are more likely to drink after transplant, directly damaging the liver as well as leading to noncompliance and failure to take necessary medications to prevent rejection. Despite the fact that this is unsubstantiated and certainly not 100% true, we happily comply with the rule. When an unrepentant alcoholic in need of a transplant comes with a willing donor, we can no longer just throw up our hands and say it's against the rules.

What about age? Almost everyone intuitively accepts the idea of a parent donating part of the liver to his or her child, whose entire life lies ahead. It has been our experience that in the reverse setting, when the parent is in need and the child is the prospective donor, the parent frequently refuses to accept the donation. In fact, a few people at the Liver Foundation got angry at the idea that a parent would ever even consider allowing such a thing. Should the equation consider life years to be gained by the recipient versus life years potentially lost by the donor?

There is still a lot of romance and mystique surrounding transplantation. Organs of dead people living on in others is about as close as we come in the world of science to reincarnation. Living donor transplants are also a subject of fascination — our early cases received great press coverage, and we met once with a filmmaker who wanted to do a documentary on the human side of living donor transplantation. As living donation becomes safer and more commonplace, however, the mystique will inevitably fade. It's a topic for a whole other discussion, but it seems a rather small step to accept living donation as a business arrangement, where the benefit to the donor is financial, much as surrogate mothers contract to bear children for infertile couples today. The American Liver Foundation recently received a letter from a prisoner offering to donate part of his liver to a person, any person, in need. Was it as a penance? In hopes of spending a week out of jail in a hospital? Should he get time off for good behavior?

I raise these questions not as an ethicist, or as a journalist, but rather as a practitioner working in somewhat uncharted territory and looking for guidance. Sometimes it all seems quite clear — but that feeling never lasts for long.

Trust and Trustworthiness in Organ Transplantation:

Good Samaritan and Emotionally Related Living Donors

ROSAMOND RHODES, PH.D.

Abstract

Organ transplantation, and living donor organ transplantation in particular, could not occur without society's trust in medicine and in transplant programs. This paper explains the importance of that trust and shows how the concept can be used to define the moral requirements for structuring organ transplant programs. The discussion goes on to outline what a trustworthy program must be, and to provide a conceptual perspective for drawing lines and setting boundaries for ethically acceptable living donor transplantation. It also explains the morally relevant considerations for accepting emotionally related or unrelated living donors.

Key Words: Living organ donor, organ transplantation, trust, ethical limitations.

THE ETHICS of living donor organ transplantation is not at all straightforward. Indeed, the practice seems to fly in the face of the medical profession's standards for ethical behavior. These standards begin with the commitment to do no harm and act for the patient's good. When an organ recipient and an organ donor are both properly viewed as patients, the obvious question is, how can it be ethical to risk one patient's well-being for the good of another? How can a mutilating procedure that inflicts risks of disability and death for the donor be justified when it does that person no physical good at all?

I would like to offer an explanation for the moral acceptability of living donor transplantation, and also propose some ethical limitations that should be placed on taking organs from living donors. The proper place to begin this analysis is at some distance from transplant issues, and with the shared understanding that doctors and medicine are committed to acting for the good of patients insofar as that good is defined by the goals of medicine. What counts as the "patient's good," and the scope of the "goals of medicine," are important issues, but will have to be bracketed and set aside for a later, fuller elaboration.

Now, to act for their patients' good, physicians have to convince their patients (that is, people who may be total or near strangers) to share information about their personal and family history and details about their symptoms that they may not be willing to share even with their most intimate relations. Furthermore, for physicians to be able to do their doctoring, patients sometimes have to appear disrobed; they have to allow their bodies to be touched and probed, even when they know that the touching is likely to involve sexually sensitive areas or is likely to hurt; they have to submit to tests that they never would have otherwise sought and take chemicals into their bodies that may have dangerous side effects; and sometimes they even allow themselves to be made unconscious so that their bodies can be invaded by knives so that body parts may be removed. To be permitted to do any of these things, albeit for the patient's good, the doctor must be "trusted."

In other words, all reasonably farsighted physicians must recognize that in order to have patients and practice medicine, they must "seek

---

Address correspondence to Rosamond Rhodes, Ph.D., Professor of Medical Education, Box 1108, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Presented at the Issues in Medical Ethics 1999 Conference at the Mount Sinai School of Medicine, New York, NY on December 10, 1999, and updated as of December 2002.

trust and deserve it." Because this rule follows from a reasonable consideration of the basic requirements for medical practice, it is the fundamental moral imperative for doctors, the ethical rule that must govern their entire practice. Every physician who considers the context of medical practice will acknowledge it. And no patient who vividly imagines the procedures that may be undertaken would want it any other way. All prospective patients (i.e., everyone) want doctors to be trustworthy. Unfortunately, medical treatment is sometimes delivered outside a climate of trust. Some patients have learned to be distrustful because of unfortunate experiences with imperfect physicians and our untrustworthy system of health care delivery. And distrustful patients do accept treatment when there is no better option. Yet such instances do not refute the claim that virtually all patients would prefer to be able to trust their doctors, and that most doctors would prefer to be trusted by their patients. And, so, all doctors must seek to promote trust and prevent its erosion.

It is also true that patients may need to, and actually do, trust doctors who are total strangers to them (e.g., in the emergency room setting or the operating theater). They trust because a history of doctors (for the most part) acting for their patients' good has (in their minds) made medicine trustworthy. Physicians today are the heirs of trust that was engendered by those who came before them, and their actions today create the legacy for those who will come after them. As beneficiaries of their predecessors' trustworthiness and as those who create the reputation that the next generation of physicians will inherit, doctors also have the responsibility of acting to ensure that the profession of medicine will have its necessary trust in the eyes of future patients.

Trustworthy Transplantation

The concept of trust dictates the necessary model for medical practice. It provides medicine with a unique set of moral rules and a distinctive rationale for defining acceptable action for the medical professional. While "trust" seems to be the defining feature of all medical specialties, the powers and privileges allowed to different specialties delineate their scope (e.g., they tell us that plastic surgery and obstetrics are part of medicine). Furthermore, the kinds of behavior that would be required to engender and maintain trust give each particular specialty its unique moral code (e.g., confidentiality is an important element of medical ethics; obedience to the chain of command is an important element of military ethics). The centrality of trust to bioethics also explains why the concept arises so frequently in the literature of medical professionals and philosophers when they address bioethical issues, although its role has not been explained (1, 2). Trust also plays a crucial role in explaining the ethics of living donor organ transplantation. The concept of trust can tell us a great deal about the characteristics that a transplant program must embody. It can also tell us a great deal about the design of transplant policies and the ethical limitations of transplantation.

Professional Competence

Because successful organ transplantation involves the collaboration of many individuals working together, a trustworthy transplant program must involve a well-staffed, cooperative team of trustworthy individuals. For these individuals to be trustworthy, they must, of course, be "knowledgeable and skilled." They must be well versed in the etiology and progress of organ failure, proficient in diagnosis, fully informed of the most recent clinical studies of pre- and post-operative management of their patient, skilled in the assessment of the likelihood of their patient having a good outcome, discerning in their evaluation of a patient's anatomy, masters of technical dexterity, practiced in operative cooperation, and accomplished in recognizing and managing bouts of rejection. Without such professional competence, neither the individuals nor the team is deserving of trust. Being knowledgeable and skilled are essential to trustworthiness and, hence, a "moral" obligation.

Caring

But team members must also be compassionate. For one thing, patients are more inclined to trust members of a transplant team who they believe genuinely "care" about their good. But beyond the psychological appeal of a caring doctor, physicians in particular need to feel caring concern for their patients' well-being in order to "merit" their patients' trust. Caring is a prophylactic against the ethical danger of making clinical judgments that reflect self-interest rather than patient interest, and it also protects against the moral hazard of doing what is easy or convenient rather than doing what one should. Furthermore, in order for patients to trust their transplant surgeons and accept their recommendations, patients need to believe that their surgeons are acting from a sense of caring rather than from selfishness (3).

Respect for Autonomy

To be trusted, members of the transplant team will also have to pay serious attention to the patient's view of what is "good." People prefer to have their own way, and when decisions are intimately concerned with a patient's own body and life, differences between alternatives can be tremendously important to that patient. Sometimes a doctor's view of what is best will be at odds with a patient's view. And in some circumstances a patient will actually consider the doctor's opinion to be utterly invalid. Because doctors need their patients' trust and because patients need to feel confident that their doctors will not impose their personal values and thereby, in the patient's eyes, cause harm, the patient's ranking of what is "good," or "respect for patient autonomy," has to be incorporated into the professional commitments of the physician.

In sum, in order for transplant teams to be trusted to a degree that allows them to act for their patients' good, they must be professionally competent, caring, and respectful of patient values. The importance of these characteristics and the actions they dictate are relatively noncontroversial. However, their relation to the need for trust in the relationship of patients to the transplant team requires deeper understanding and some creative application of the concepts.

Trust and Living Organ Donation

To be trusted by transplant recipients, transplant teams must be competent and skilled, caring, and respectful of patient autonomy. But to perform surgery on a living organ donor who needs no surgery, and to remove a vital organ or a piece of a vital organ from that donor for the benefit of another, the team must do more and be more. Regardless of how intensely a donor cares about the survival of the recipient, a donor has to be assured that s/he has more than a reasonable chance of surviving the donation and avoiding serious complications. And for living donation to be or become an acceptable approach to managing another person's organ failure, the transplant community has to demonstrate that it can be trusted not to subject donors to unreasonable risks.

Within the relationship of an individual donor and those who offer to perform living organ donation, a trustworthy team has to be honest in their estimates of the risks and harms, and forthright in their communication about their own experience and skills. These are the standard requirements of informed consent. But when living organ donation is recommended as a standard option for managing end-stage organ failure, the trustworthiness of the transplant community and the trustworthiness of their recommendations is even more crucial. Because living organ donation subjects healthy people to the harms and risks of radical surgery that does them no physical good, as a medical "institution," transplantation can only maintain its trustworthiness and continue to perform its procedures if it restricts living donor transplantation to situations where there is only a very small likelihood of serious and enduring harm to the donor.

So, when transplanters judge the risks to be unreasonable — when the chance of a donor's safe survival is low — no matter how much a donor might want to give, and irrespective of the donor being informed and accepting the risks, transplanters must not put that donor in jeopardy. In other words, transplant programs must impose strict limitations on donor choice out of concern for maintaining the trustworthiness of the transplant community.

In kidney transplantation, we have had instances of parents who have wanted to donate one of their kidneys in order to spare a child the burdens and disabilities associated with dialysis. In heart transplantation there have been instances of parents who have sincerely offered to be sacrificed to save their child. Surgeons have rightly refused to perform such operations. Preserving the trustworthiness of living organ donation justifies their stance. The practice of living organ donation could not be tolerated without the assurance of the transplant community that the surgery would not be performed when the benefit is less than survival or when the donor risk is too great. Only transplanters have the ability to make such assessments, and society trusts them to hold the line at reasonable risk.

Good Samaritan Organ Donors

The standard for ethically acceptable living organ donation is the reasonable chance for a worthwhile result and the reasonable chance of doing no more than what would be acceptable when there are strong emotional ties to the recipient. A Good Samaritan who comes forward to donate an organ to an individual who is unknown to him or her raises the question of whether living organ donation can be acceptable without strong emotional ties to a particular recipient. Such generosity and courage invite questions about the Good Samaritan donor's capacity to make the decision.

In other contexts extraordinary generosity and courage are praised and revered. Yet here, the same characteristics invite deep suspicion and a mental health examination. This is strange.

In an ethics committee conversation about this issue, Dr. Richard Stein suggested that we consider a particular forest in Israel. I believe that Dr. Stein was referring to the forest that commemorates those non-Jews who risked their lives, families, social standing, careers, and resources to rescue Jews during the Holocaust. The trees in that Israeli forest represent an extraordinarily generous and courageous few, in comparison to the vastly more numerous others who were less generous and courageous. To us, those few are heroes, not the mentally impaired.

Dr. Stein's apt analogy encourages us to take another look at Good Samaritan organ donors and to resist disparaging their motives or mental health. On the other hand, the comparison fails to capture an important and disanalogous feature of Good Samaritan organ donation. While some heroes of the Holocaust acted as individuals to achieve their goals, Good Samaritan organ donors require the cooperation of a transplant team. The team must consider to what extent its participation will maintain the trustworthiness of the transplant community. So, while the high likelihood of a good recipient outcome and the low likelihood of seriously jeopardizing the donor should be the same standard for emotionally related and unrelated organ donors, extra scrutiny into the motivation and reasons for Good Samaritan donation should be required, out of concern for preserving the trustworthiness of the transplantation community.

Conclusion

By starting with the commitment of the physicians to act for their patients' good, I argued that doctors and transplant teams could not do their work without having the trust of their patients and organ donors. Because trust is the necessary condition for medical practice and transplantation, reasonable physicians and transplant teams have to recognize that they must seek trust and deserve it, and adopt that as the creed for guiding their transplant decisions and their programmatic policies. Trust is the fundamental moral law for medicine and the justification for the standards and practices of transplantation.

While the trust approach reveals certain guiding principles for transplantation, it does not end ethical discussion or rule out moral disputes. Nevertheless, trust does offer a way for sorting out differences, a guiding principle for adjudicating moral conflicts in transplant policy, and the framework for balancing competing considerations. It directs transplant programs to resolve moral conflicts by trying to maximize trust and minimize damage to trust. In sum, the trust approach to the ethical issues in transplantation identifies some considerations that are not otherwise appreciated and it provides a justification for policies that are essential for the ongoing practice of transplantation, but are not otherwise comprehensible. For these reasons and because of its intuitive force, the trust-seeking perspective should be embraced as the guiding moral theory for the ethical practice of transplantation.

References

1. Caplan AL. Odds and ends: trust and the debate over medical futility. Ann Intern Med 1996; 125(8):688–689.
2. Lantos JD. Futility assessments and the doctor-patient relationship. J Am Geriatr Soc 1994; 42(8):868–870.
3. Rhodes R. Love thy patient: justice, caring and the doctor-patient relationship. Camb Q Healthc Ethics 1995; 4(4):434–447.

Panel Discussion

Morning Panel Discussion

Audience:
I have two questions about the stem cell presentation. You had mentioned that you need to use colony-stimulating factors (CSF), which raises ethical issues. I'm not clear what those issues are in the case of getting a blood sample. Also, you alluded to informed consent for getting cord blood. Why isn't it fairly straightforward? Why isn't the mother able to consent for cord blood?

Dr. Steven Fruchtman:
In answer to your first question, CSF stimulates the normal bone marrow. The concern is long-term safety. CSF is a natural substance that our own bodies make. We're using it in very high pharmacological doses. Can it stimulate things we don't want to stimulate — like leukemia and things of that nature? There are no data. It appears safe, but its use has only recently begun.

In answer to your second question, I didn't say there weren't solutions to the ethical dilemmas of cord blood consent—there are. The person to ask, clearly, is the mother, and perhaps the father should be involved in the discussion. Questions arise about when to obtain informed consent. Clearly, you can't do it at the time of labor. Can you get consent after the delivery? It's a timing issue. All these things need to be discussed.

Audience:
There are human drives that apply to all kinds of transplants. Up until a certain point, a person has lived with all the faculties and features of a natural and healthy body. The drive to maintain that is very natural. Is there any comment on that?

Dr. Michael Hausman:
Well I agree with you that there certainly is a desire to maintain a normal body. The issue is: Will transplantation of a hand achieve that end? If the hand or body part is insensate, it's not functional. This is currently an insurmountable problem. Until we can restore sensation, we're not really restoring function. With larynx transplantation, in order to vocalize, you need the arytenoid muscles and their functional nerve supply. How do you get around that problem? While the muscles can be transplanted, the motor nerves have to grow back so that the muscles can be re-enervated.

Dr. Eric Genden:
That's probably the single largest problem that we have. It's actually not the re-enervation, because as you know, in St. Louis we performed a number of clinical nerve transplants that have turned out quite well and we've done them in a laboratory without any problem. Even in the laboratory the problem is an issue of actually directing the fibers and the kinesis that occurs. We're actually able to restore sensation in the nerves. It's the motor function, direct motor function, that's the biggest problem we face right now.

Audience:
Is there a distinction between the ethical issues raised by cosmetic surgery and those raised by transplantation? Is it simply the immunosuppressant drugs and their long-term effect? Is it the great amount of resources, compared to the typical costs of cosmetic surgery? Or is it the fear that transplantation surgery is likely to be considered more of an entitlement that the HMOs might have to support? Just what is the distinction between why we seem to accept cosmetic surgery but find transplantation problematic?

Dr. George Agich:
With respect to transplantation, we're in a socially charged area because standard transplantation has been directed toward life saving. It seems that we're distorting that rescue function by introducing, sort of engrafting onto it, what looks like a cosmetic function. That sets the context of this "non-vital" and "vital" distinction, which, as I argued, is not a very compelling distinction in the end.

Afternoon Panel Discussion

Dr. Myron Schwartz:
Dr. Rhodes, you raise the issues of recipient selection and the autonomy of the donor to decide whether the risks are worth taking. From your discussion I got the sense that in order to maintain the trustworthiness of the community, we

should take into account the view of the average person on the street on what would be unreasonable or not worthwhile. As transplant surgeons, we should not agree to transplant patients when the likelihood of success of the transplant is low, even though that particular donor may think it's okay. Is it safe to say that we'd be doing something that would cause us to lose trust in the public eye?

Dr. Rhodes:
Approximately. I think this is hard to get exactly right. I think the perception of the community is very important. I don't know if I'd put it in terms of the average person on the street, but rather a reasonable person. What would a reasonable person think is acceptable? When you're in the field you might get a slanted view — you see the urgency of your patients' needs. I think that keeping the options open to public debate and trying to get a communal sense of what is acceptable are important. On the other hand, transplant surgeons know the most about what makes something risky or likely to succeed. So, the idea is for surgeons to make the decisions, guided by the idea of how the public would respond to the decisions if they knew what we were really doing. I don't want the public making the decisions. I would like you to make the decisions, but keep that idea in mind. Does that make any sense?

Dr. Schwartz:
You don't want the public to think that we're crazy, making outlandish decisions.

Dr. Rhodes:
I think the public needs to trust that you're doing reasonable things.

Dr. Sheiner:
I can see it turned around, where the transplant surgeon should be like the Supreme Court in a sense, to judge the pulse of the nation.

Dr. Rhodes:
It's more like what goes on in recipient review committees, of which we're all part. We have a discussion and every once in a while somebody might say something like, "If this made it to the five o'clock news, what would people think"? That idea should be in the back of your mind, informing or playing a part in your decision. Because you know the most about all the technical features and the likelihood of success, I think the decision should be made by you.

Dr. Sheiner:
It could all be turned around. I can see on the front page of the *New York Post*, "Mount Sinai Refuses to Perform Potentially Life-Saving Surgery." It is hard to determine how that 10% chance of success is going to be perceived by the public. I think it's hard.

Dr. Rhodes:
Maybe what I said didn't make complete sense because you're only seeing a piece of this elephant. What I spoke about today comes from a general view of professions. That there is the morality of society, and then society gives different professions authority over certain activities, over certain powers that it gives to no one else. It gives surgeons the authority over cutting into people. It doesn't let philosophers cut into people, only surgeons. These special powers go along with the trust to use them for our good. Because they have the knowledge and the understanding, I think surgeons should make the decisions about when to perform a transplant. But they need to keep an eye on the purpose for which society has entrusted them with these special powers. Transplant surgeons' view of how to dispense and use their powers has to be focused back on what powers society has given to them. It's this mutual regard between society and the profession, and the profession and society, that should determine the limits. That's not in any way like making a decision by poll. Public discussion might influence the surgeons' discussions. I am sometimes privileged to be part of the surgeons' discussions, and I can get to ask extra questions. But I think the decisions are their job.

Dr. Agich:
If the patient (the recipient) is so sick that the chances of benefit diminish, then we should have much higher standards for donor consent and we should have greater reluctance to subject them to the risk. That would make a good argument for restricting live donations to patients who are relatively healthier and who stand to benefit.

Dr. Sheiner:
In reality, what we have learned is that sicker patients do not do as well as healthier ones with living donation. In fact, we will not consider someone who is status 2A (gravely ill and likely to die in the next week or two) to be a living donor candidate. The caveat is whether they are high enough on the waiting list to have a rea-

sonable chance of getting an organ. That gives us a little bit of comfort. We do not perform living donations for the sicker patients.

Dr. Agich:
That may give you comfort, but I would suggest that even when a patient isn't high on the list, subjecting a donor to the risk where the chance of benefit is low might not be ethical.

Dr. Sheiner:
I think we are coming to that belief as well.

Dr. Agich:
I'd like to ask the panel to comment on how you assess donors. One of the questions we're facing at the Cleveland Clinic, with respect to the live donor program we started, is how to assess donors for motivation. The notion that somebody needs to be a rational consenter is very problematic when you have close connections, affiliation and love for a family member. What are you doing in terms of assessment of donors, and how are psychiatric and psychosocial assessments used in the donation process?

Dr. Schwartz:
Apart from medical and laboratory studies, our patients are seen by a social worker and discussed. We presume, in a situation where there is a family relationship, if there's no obvious problem, that there is a legitimate basis for donation. I don't really have the sense that we're doing in-depth psychological profiling and trying to fish for possible underlying things. I'm not sure whether our approach is right, but our approach in the adult liver transplant program is that we have a talk with the donors, the surgeons talk with them, the medical people talk with them, the social worker talks with them, and if there's nothing glaring and there's a relationship with friend or family, we go ahead. There's certainly no forensic psychological testing or anything like that.

Dr. Rhodes:
I know a lot of bioethicists become concerned, to the point of hysteria, about people who are deeply emotionally connected not being able to give informed consent. They see the situation as too coercive. Personally, I think this is craziness. We act largely ruled by what we care about most, so our values are supposed to inform our choices. From the point of view of respect for autonomy, I think that it's tremendously paternalistic to look at people with the presumption that because of their emotional involvement they have lost their capacity to consent. Out of respect, we owe it to people to start with the presumption that they have the ability to consent unless they do something or say something that makes us deeply suspicious. So, as a starting point, I would start at the other end. Presume that family members have the capacity to consent and don't be unduly suspicious unless they raise red flags.

Dr. Schwartz:
I'd have to say that's been our approach.

Audience:
I think that's what's very special about the ethics of medical transplantation, and it is illuminated by Dr. Rhodes' remarks. I don't think that it works without acceptance and trust. Usually the physician is the advocate for one particular patient. But in living donor transplantation, the physician has to choose to be either an advocate for one particular patient or for the patient and the donor, therefore two patients. If all of these participants, particularly the donor and the physician, work on the basis of trust, I don't think that people would complain. But unless that aura exists in the public's mind, there wouldn't be a transplant community. Given that, it seems to me that a reasonable person is concerned with whether the physician has a good procedure — that the science works. Because if the science didn't work, one wouldn't want to participate.

Dr. Schwartz:
We have lots of patients dying on our waiting list. We approached transplantation using live donors with a lot of reluctance. We didn't get into it earlier despite our expertise and experience in the type of surgery that needed to be done in a donor operation and a recipient operation. We were worried about it. But, ultimately there's no question that we got into it because, week after week, two or three patients were dying on the waiting list. Between 60 and 70 patients died last year. It was concern for our patients that got us into living donor transplantation. We've now reached the point where we're advocates of the procedure. I don't think I can deny that.

We are advocates of this procedure around the country. We're asked to speak about it and are looking for applications of the technology. Sometimes we stretch the criteria to allow a donor to donate and we accept cases where the likelihood of success is relatively low, because there is nothing else to do. We have to think about the trust issue. Clearly, we are advocates for the procedure at this point. I think we are all concerned about the donors, and the first thing we all say is donor safety is paramount. But we need to have sessions like this every so often to get our bearings, because it is easy to get carried away with it.

Dr. Sheiner:
I think there's been a shift, at least in my mind. When we first started living donor transplantation, I thought that to justify living related donation, the recipient outcome should be better than for cadaveric transplantation. And now, within a very short period, we're talking about giving the high-risk group a chance. That's a major shift. We have become advocates of the procedure. I hope that we don't end up with a complication that makes us sit back and think again.

Dr. Thomas Fishbein:
I do not believe that I am an advocate for the procedure. I think that we do both the donor and the recipient operations with the same team, as opposed to having a dispassionate and separate team do donor surgery that has nothing to do with the transplant. We are the advocates for two patients and we have an equally important role in advocating for both the donor and the recipient. The operation is a vehicle to produce an end result for both the donor and the recipient. For the recipient it is to gain a second chance at life. For the donor, it is a chance to save the life of someone who the donor has cherished. The donor values the emotional benefit that they get from the recipient. And so, the more impassioned and the closer the relationship of the donor to the recipient, the less suspicious I am. I believe that it is probably more rational to accept a lower chance of success when the relationship between the donor and the recipient is closer. For example, a child who needs a bowel transplant (because that happened to be my example today), has a 30% or 40% chance of dying. Yet, it's the mother or the father who is deeply invested in the child. Maybe it's an only child. Maybe the parents have an infertility problem. They have a great and a very impassioned investment. I would advocate that we should accept a 40% chance of failure or even a 50% chance of failure in that instance, because, in fact, the benefit to the donor is greater if there is success.

Audience:
This is indeed an outstanding conference for questioning the big divide between transplantation for saving life and transplantation for quality of life. The average person still believes there's a big difference. This conference has focused on this subject and pointed out very clearly, based on the science, and even more important, on the ethics, that there's no big distinction. With time and improved technology, the distinction will collapse. This meeting is truly historic.

Dr. Sheiner:
One of the things we have learned is that hepatitis C, one of the diseases for which we transplant, recurs. We have many patients who are in need of a second transplant, and we have a few who now need a third transplant. I think the biggest problem has been that we have become these patients' advocates. We have known them for five years or more, as opposed to the patients waiting on the list who we do not see as often because they're under the care of another physician. We have to really start looking at results. Transplant organs are a scarce resource. We have learned to say that some people are too sick to be listed. Yet we know that we sometimes get a young patient who we'll transplant even though he looks too sick. As we have looked at our results, we have tried to identify criteria, such as renal failure and degree of illness, that may help us predict who should and who should not be transplanted. We have to start making some hard decisions, which, in the past, we were reluctant to do.

Dr. Schwartz:
There are many factors that go along with having a transplant that may play into how well the second one or the third one will work. I don't know that having had a previous transplant, in and of itself, is an independent risk factor. It's just that it goes along with a lot of other things that can make things harder. There are cases where it is very clear that the transplant has a high likelihood of succeeding. The real issue is that we have to be honest with ourselves, and I don't know that we can totally discount the bond. We have to work to keep the patients who have had transplants alive. We have always looked at transplantation as a trust issue. We are trusted not to abandon the patients who we have already transplanted. Obviously, if there's no chance of success then it shouldn't be done. But I think that a lower chance of success is acceptable, and that has something to do with trust.

Dr. Sheiner:
We have to re-evaluate our threshold just because the number of patients on the list who are dying is increasing. At this point one question is: Should we give more people a first chance, as opposed to maintaining people who've already had their chance? It would be hard for me to take that position, but we may have to do it as the number of deaths increases.

Dr. Schwartz:
We talk about the possibility of living donor transplantation with most patients who are at a point where they need a liver transplant. We mention it and we don't push it. Certain patients, those who have tumors for example, cannot wait to get an organ. If they don't get a transplant relatively soon, which practically speaking means that if they don't have a living donor, they're not going to get transplanted. In those cases we'll push a little bit more. But basically, at the first interview, we just mention that living donor transplantation is an option. Those who come back asking for the procedure are the ones who have discussed this possibility with their family. By the time the family comes forward with a potential donor, these issues have been resolved. It's not something that we talk about much with them here at our center.

Dr. Sheiner:
If in private discussions, with either the coordinator or the social worker, there is some donor reluctance, we've always offered a medical "out." We'll say that for medical reasons the person is not a donor. We have to worry about the donor who's afraid of causing some sort of conflict by saying no. If we sense a hesitancy, we have offered to say that they are medically unsuitable. There is a level of coercion that is not always clear, but I think you have to allow the potential donor to have an "out" if it becomes clear that the person is not as eager to donate as the other family members believe. We have done that.

Audience:
Today the risk for a kidney donor is 1 or 2 per 10,000, and the risk for a liver donor may be higher. We know also that people are killed in plane crashes and auto accidents. We have figures for these. People may have a hard time ranking the risks of organ donation, so it might be useful to give a donor the context of the risk.

I want to raise the "reasonable person" standard. Could we say that what a reasonable person would choose should guide the policy?

Dr. Rhodes:
Well, I want not just wise people from the general public. I want the decisions to rest with the wise and informed people who actually have the responsibility on their hands.

Audience:
In terms of the risks for the donor, let's say it is 10%. Is that an acceptable risk for a donor or is that not?

Dr. Rhodes:
I want the transplant surgeons to figure it out. When they decide this is reasonable, then they could say, "In your case we can offer you living organ donation if there is someone in your family who would want to come forward." And if the surgeons decide a 10% chance of survival is too small, they shouldn't mention the option of using a living donor.

Audience:
I'm talking about the risk to the donor.

Dr. Rhodes:
Okay, the risk to the donor. If the surgeons evaluate the donor and they decide that there is a 10% risk of death or serious injury during donation and that it is too high a risk, I want them to say, "I know you very much care about your granddaughter, but you are not medically acceptable." I think the transplant surgeons are the ones who have to draw the line at what is reasonable for both the donor and the recipient. They're the ones who have to hold the line. They do not have the trust of the public unless they do that. So you can have the grandmother, the very committed grandmother, who says, "My life is worth nothing to me. I don't care about a 10% chance of dying. It's not worth anything to me if my granddaughter dies." And if the transplant surgeons think that a 10% chance of her dying is too great, they have to say, "We sympathize with you. We understand. We cannot do this. This is not something that our professional responsibility will accept. We cannot do it." And when they say, "We cannot do it," they should not mean, "Well, go to Pittsburgh or Minnesota and maybe they'll do it." What they should mean is that no reasonable physician should do it. No transplant program anywhere should do it, because it doesn't conform with what reasonable surgeons should accept.

Dr. Schwartz:
I think I would much rather be able to tell the

Ethics Committee I can do this procedure with 1% chance of mortality. Tell me, Ethics Committee, is this the right thing to do or not? What makes me, as a surgeon, the appropriate person to decide whether the results are good enough to be acceptable?

Dr. Rhodes:
I wouldn't disagree with you. If you're going to the Ethics Committee here at Sinai you are still not going to the public. You're saying, "Here we have a case that we think is really tough. We'd like some help with it from our peers. We want to get a more informed consensus. Realizing that we want to push the envelope, we might be aggrandizing the program We're not sure that our judgment is on target. We want some help." That's a very appropriate use for an institutional ethics committee. But it's very different from saying let the public take a vote.

Audience:
How can one person get more than one transplant when there are other people on the list? I don't understand that.

Dr. Schwartz:
The sicker person on the list gets the transplant. Someone who has not had a transplant may not be as sick as someone who has previously had a transplant and now needs another one. When an organ becomes available, it will go to the patient who is sicker. If the patient who hasn't had the first chance yet is sicker than the person who has had a previous transplant, then the re-transplant patient will not get the organ. By and large, the way we have viewed things here is that there is no difference in the way that we would look at someone for a first, second or ninth time.

Even with a reasonable chance of success, a patient can reject an organ for many reasons. It doesn't necessarily mean that the patient didn't take their medication, or is a bad person, or was a poor candidate. It can just be that they happen to have a really strong immune system, and even though we gave them a lot of medication, they were stronger. So it's the medical opinion of whether you have a reasonable chance of success that is the first decision that gets made here. Certainly that is not the case everywhere. Surgeons I've talked to in other centers said that when they offer someone a transplant they tell them up front, "If it comes to needing a second transplant, you can't get one here." That's not been the approach that we have taken at Mount Sinai.

Dr. Sheiner:
I think what you were asking is, if you reject a liver once, are you likely to reject the second liver? That's not what we see in liver transplants. The most common reason for needing a second transplant is rejection. Interestingly, in liver transplantation, you are not more likely to reject a second time than you were with your first transplant. The biggest problems we get into are technical. Patients who have been on steroids are actually more likely to get infections. We end up losing them in the perioperative stage — we don't lose them down the line to recurrence of the same problem that they had the first time. So if you rejected your first liver seriously enough to need a second transplant, there is no greater probability that you're going to reject your second liver. So the decision focuses on whether the patient is well enough to get through the perioperative period. We are not particularly worried about whether they are going to reject that liver again.

Audience:
Dr. Rhodes, your argument has nothing to do with the donor's acceptance of risk. It's really about whether the physicians, with their professional responsibilities, are able to take that risk. You transfer the argument onto what is doable by the physician.

Audience:
For the physicians, suppose you could in fact take into consideration all of the risk and prognostic factors, and somebody could manufacture a curve that would identity the recipient with the highest probability of the longest life of everybody on the list for this organ. Would you be willing to use that in allocating organs?

Dr. Lewis Burrows:
In kidney transplant, obviously there is an option. If someone cannot be transplanted, that person can be maintained on dialysis. The way we choose who receives the cadaver organ is a rather complex procedure. It's partly based on waiting time, but it's partly based on matching.

Dr. Sheiner:
In liver transplantation, we are learning that there is recurrence of disease. So if I had a patient with hepatitis C who is going to live a year without transplant, even though I thought I could get him out of the hospital in five days with a liver transplant, I wouldn't transplant him because I'd be concerned that he could

come back two years from now with worse recurring disease and a poorer quality of life. Decision making has gotten even more complicated now that liver transplant for 40% of our patients is not a cure. It prevents them from dying, but they have a 50% chance of getting recurrent disease.

Dr. Fishbein:
A formula that could identify the best patient would be great, but it would be a pretty complex formula. It would have to take into account a lot of things besides just post-transplant survival.

Dr. Schwartz:
In the year that Dr. Starzel attempted the first "insane liver transplant" and was on the cover of *Time Magazine*, he was popularly derided as an evil doctor who was killing patients without mercy. Yet in this short time span, we are now doing thousands of liver transplants per year. When cyclosporin came out, it completely changed the face of transplantation, one month before it was even available. When the next generation of anti-rejection drugs came out, they completely changed the course of losing organs to chronic rejection and having to do re-transplants. Now we have living transplantation. Something else is going to come out later. So, letting people die by using wartime triage philosophy may turn out to have been a mistake when, a month later, something new is discovered.

Dr. Rhodes:
In wartime triage, you're not transplanting the patients who are the sickest. You're still not doing them. One of the things you actually tell patients is, "We're listing you, but if you become too sick because of the low chance of survival, we won't transplant you." Wartime is still an operative principal of your program.

Dr. Sheiner:
There is still a concept "too sick to transplant." You have to have a reasonable chance of survival.

Dr. Rhodes:
Right, a reasonable chance of survival. The idea is that once you rule out the group that is too sick to transplant, maybe the difference between the rest is not significant enough to make any other distinctions between them.

Severe Asthma:

Epidemiology, Pathophysiology and Treatment

Sally Wenzel, M.D.

Abstract

Severe asthma is poorly understood clinically, physiologically and pathologically. Whereas milder forms of asthma are generally easily treated, more severe forms often remain refractory to the best current medical care. Although some asthmatics have been severely affected for most of their lives, there appears to be a second group that develops severe disease in adulthood. Additionally, it is not clear which genetic and environmental elements may be most important in the development of severe disease. Physiologically, these patients often have airtrapping and may have loss of elastic recoil, as well. The pathology demonstrates a heterogeneity of findings, including continued eosinophilic inflammation, structural changes, and distal disease. Treatment is problematic and will probably remain so until a better understanding of this disease develops.

Key Words: Asthma, physiology, inflammation, remodeling, treatment, phenotypes.

Severe or refractory asthma afflicts a small percentage (probably less than 5%) of the asthma population. Since these patients remain difficult to treat and prone to severe exacerbations, they contribute disproportionately to the overall costs of asthma. The introduction of high-potency inhaled corticosteroids (CS) markedly decreased the number of patients dependent on oral CS. However, little further progress has been made in understanding the disease and improving its treatment.

Definitions

Severe, persistent asthma has been defined in recent guidelines, but the definitions have been somewhat limited in scope and difficult to apply. Severe or "refractory" asthma was given a working definition by an American Thoracic Society sponsored workshop, the proceedings of which were published in 2000 (1). The definition of persistent asthma requires that either one of two major criteria (continuous high-dose inhaled CS or oral CS for more than 50% of the previous year) be present, with 2 of 7 additional minor criteria required. The minor criteria include evidence for obstructed lung function, exacerbations, disease stability and amount of additional medications. Patients must also have had compliance and exacerbating factors fully addressed. The presence of these refractory asthmatics in the asthmatic population was recently confirmed in the entry data from a long-term prospective study of 5000 "difficult-to-treat" asthmatics. These patients were seen in asthma offices across the United States and were receiving "optimal" therapy according to recent guidelines. In this population of subjects, in the previous 3 months, approximately 10% had required a hospitalization, 20% had gone to the emergency room and 40% had received a steroid burst (2). The actual numbers of these patients or their percentage within the larger asthma population is not clear.

Epidemiology and Natural History

Little is known about the development of severe asthma. Do most severe asthmatics have a life-altering event in childhood that irreversibly alters their lungs, or do they slowly but

---

From the National Jewish Medical and Research Center, Denver, CO.

Address all correspondence to Sally Wenzel, M.D., National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206; E-mail: wenzels@njc.org

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY, on December 11, 2001, and updated as of August 2002.

steadily decline over the years? Did those with a history of "adult-onset" disease actually have some level of childhood asthma that was ignored, or did they have a more rapid decline in function once the asthma began? None of these questions has been satisfactorily answered. Some information comes from the large cohort of asthmatics from Melbourne, Australia which has been followed for 35 years (3). Those data suggest that if you have reduced lung function in childhood, you are likely to have reduced lung function in adulthood as well, but there is little "progressive decline" in the mean data. Interestingly, two studies from Europe suggest that late-onset asthma is associated with a more rapid decline in lung function (4, 5). In the data base of more than 100 severe asthmatics seen at the National Jewish Medical and Research Center, approximately two-thirds had onset in childhood, the remaining one-third after the age of 20 years (6). Whether there are distinct phenotypic differences in adult vs childhood-onset asthma or severe asthma is not known.

Risk Factors

As with many other diseases, asthma risk factors can be divided into genetic and environmental factors (Table 1). Unfortunately, asthma is a disease involving multiple genes. Severe asthma is probably not different and is less well studied. There are reports of relevant mutations in both the IL-4 gene and the IL-4 receptor; some of these mutations have been linked to loss of lung function, others to near-fatal events (7, 8). Two potential remodeling factors, transforming growth factor (TGF)-ß1 and monocyte chemotactic protein (MCP)-1, both of which can promote fibrotic reactions (9, 10), have also been associated with severity of asthma. Whether mutations of the receptors for the primary treatments for asthma (beta$_2$ and glucocorticoid receptors) could conceivably decrease responsiveness to medications and influence outcomes is not yet clear.

TABLE 1

Factors Controlling Asthma Severity

1. Genetic factors (Th2, remodeling, response to drugs)
2. Continued allergen/tobacco exposure
3. Infection (RSV, *Chlamydia*, *Mycoplasma*)
4. Intercurrent sinusitis/GERD
5. Obesity
6. Compliance/Adherence

RSV = respiratory syncytial virus
GERD = gastroesophageal reflux disease

Environmental factors include both allergen and tobacco exposure, with the strongest reactions occurring in response to house dust mite, cockroach and *Alternaria* exposures (11 – 13). Additionally, many patients will continue to smoke or own a cat despite being aware of the negative effects (14). Infection may also contribute to severe disease. Respiratory syncytial virus infections are implicated in children, and pathogens such as *Mycoplasma* and *Chlamydia* may play a role in adults (5, 15). Although not precisely "environmental," additional "lung-external" factors may include obesity, gastroesophageal reflux disease (GERD) and chronic sinusitis. Probably all severe asthmatics should have a pH probe at some point to test for silent GERD. However, data to support an improvement in symptoms after proton pump inhibitor therapy in this population are not available. The large-scale epidemiologic study of severe/difficult-to-treat asthmatics (6) also suggests that body mass index increases with increasing severity of disease. Seventy-six percent of that severe cohort were either overweight or obese (16). Obesity can also be linked to obstructive sleep apnea, and overweight asthmatics should probably be evaluated for this. However, similarly to GERD and chronic sinusitis, the relationship between effective treatment of obesity (and accompanying sleep apnea) and severity of disease is not clear.

Certainly another "external factor" related to severity is compliance/adherence to medications. Studies have suggested that for children and adolescents, instability of disease is related to lack of adherence to CS therapy (17). However, there are other patients whose current medications do not effectively treat the disease. For those patients, lack of adherence to medication may be influenced by lack of responsiveness to medication, but further study is required in the severe population to determine the proportions of each. If the patient is on oral CS, an early morning cortisol level can be helpful in determining compliance. If concern remains, then treatment trials with injectable long-acting steroids, such as depomethylprednisolone or triamcinolone, can be informative (18).

Physiologic Aspects

Although forced expiratory volume in one second (FEV$_1$), the classic measure of airflow limitation, has been commonly used to indicate the presence of "severe" disease, it is clear that the correlation between FEV_1 and disease symptoms is poor (19). While airflow limitation occurs during physiologic changes of severe asthma, it is probably only a part of the total picture (Table 2). One prevalent theory regarding severe asthma is that it develops due to progressive limitation in airflow, which is often presumed to be "irreversible." Although this may be true for some patients, others may have severe airflow limitation at presentation, while yet others, primarily adults, may develop a more rapid decline in lung function over a 10-year (or less) period of time (5). Finally, whether these changes are truly irreversible, or whether there is irreversibility as a result of current aggressive medical management, is not clear.

Changes in airway reactivity also play a role in the severity of asthma, but correlations of 20% decrease in FEV_1 (PC20) with disease severity, though present, are poor (20). Increased airway reactivity probably relates to stability of airflow, hence variability in peak flow/FEV_1. This "instability" may be an important aspect in the symptomatology of a subgroup of severe asthmatics, where continuous airflow limitation may play a more minor role (21).

It is conceivable that other physiologic factors, such as changes in elastic recoil and/or small airway physiology, are also important. For years, it has been observed that elastic recoil properties of the lungs in asthmatics are not normal (22, 23). General lung compliance appears to be increased in patients with moderate persistent asthma (24). There are also suggestions that the airways (in addition to parenchyma) may be more collapsible than normal (25). Those asthmatics with more collapsible airways also appear to be at a higher risk of near-fatal events.

There is also considerable evidence for airtrapping in severe asthma, without associated hyperinflation. Residual volumes are routinely more than 200% of what is predicted in severe asthma, with only modestly increased thoracic gas volumes (25). Whether this increase in residual volume is reflective of small airway disease is not known. However, it is likely to contribute to changes in elastic recoil.

TABLE 2
Physiology of "Refractory Asthma"

1. Ongoing airflow limitation with incomplete reversibility
2. Airtrapping — ↑ in RV
3. Lability/reactivity
4. Collapsibility

RV = residual volume

Pathology of Severe Asthma

Unlike many other diseases, the pathology of asthma, and severe asthma in particular, remains poorly understood, primarily due to limitations in tissue availability. Given the heterogeneity of the presentation and the physiology, it is likely that heterogeneity exists at the pathologic level as well.

Many different pathologic explanations for severe asthma could certainly exist, but at least four possible pathologic explanations have some supporting evidence (Table 3). It is obvious that, although different, these explanations may overlap as well.

Poor/Altered Response to Medications

Pathologic studies of severe asthma suggest that up to two-thirds of severe asthmatics have persistent tissue eosinophils, despite continued high-dose systemic steroids. In addition to high numbers of eosinophils, there are associated increases in T lymphocytes and markers for activation of a Th-2 type of pathway (25). This pattern of inflammation may be thought of as representing the "classic" form of steroid resistance, where a Th-2 type pattern of inflammation persists despite the presence of high-dose steroids. The mechanisms underlying this lack of effect may include abnormally high levels of pro-inflammatory mediators sequestering the glucocorticoid receptor (GR), diminished binding of the GR to the genome, or increased levels of an alternatively spliced GR (GR-ß) which has decreased inhibitory capabilities (26–28). However, it is possible that other, non-Th-2 pro-eosinophilic, factors also play a role in the process.

Airway/Parenchymal Remodeling

In the last 5 years, it has been suggested that the apparent progressive loss of lung function in

TABLE 3
Pathologic Explanations

1. Altered response to medications
   "Steroid resistance"
2. Structural changes in airways
3. Distal location of disease
4. Difference in underlying pathology

more severe forms of asthma is due to structural or remodeling changes in the airways (and perhaps) parenchyma. Although the precise changes remain unclear, implicated structures include the subbasement membrane (SBM), epithelium, smooth muscle, nerves and blood vessels.

Perhaps the best studied of these structures is the SBM. Although the SBM has been reported to be thickened in asthma, its relationship to disease severity is unclear. In a study referred to above (25), severe asthmatics with persistent eosinophils had the thickest SBM when compared to normal controls, milder asthmatics and those without eosinophils. However, the absolute increase in thickness is small and not likely to explain the increase in airflow limitation. It may, however, be a marker for abnormalities in composition, distribution or quantity of extracellular matrix elements in other regions of the airway or parenchyma, which are not as easily identified.

The epithelium is almost certainly abnormal in asthma, with an increase in the goblet to ciliated epithelial cell ratio. Subsequent mucus plugging of the small and medium airways probably contributes to airflow limitation and airtrapping in severe asthma. Early studies suggest that two pathways — epithelial growth factor receptor and transforming growth factor-ß1 and/or ß2 — may be altered in asthma and contribute to an inappropriate and inadequate repair process, augmenting goblet cell metaplasia and mucus production (29, 30).

The amount (and perhaps phenotypes) of smooth muscle in the airways of severe asthmatics has also been reported to be increased. In one study, patients dying of status asthmaticus had increased smooth muscle mass in the airways, from the largest airways to nearly the smallest (31).

It is likely that alterations exist in the alveolar attachments to the airways and in the airways themselves, which contribute to collapsibility of the airways. Elastin has been shown to be abnormal (decreased or disordered) in patients who died of asthma. Further, proteolytic enzymes which alter elastin composition have been shown to be increased in several instances in asthma (32, 33). It may be that changes in elastin composition, secondary to chronic inflammatory elements, contribute to the unique structural/functional relationships of severe asthma.

Distal Location of Disease

Physiologic and pathologic data suggest that inflammatory changes exist in the lung periphery (Figure). Although its relationship to severity of disease remains unclear, autopsy studies have suggested that both increased inflammation and increased wall thickness exist in patients who died of asthma, as opposed to milder asthmatic and normal controls (34, 35). Recent studies of living asthmatics have also suggested that distal lung inflammation may be more important than proximal inflammation, with mast cells contributing significantly to that process (36, 37). These data have considerable implications for current drug therapy, as most inhaled medications are unlikely to reach the lung periphery in high amounts (38). Finally, structural and inflammatory changes may occur to a greater degree in the small airways, due to the smaller general mass of the airway structure and the lack of supporting cartilage as compared to large airways.

A Different Underlying Disease

Numerous other diseases could meet these basic physiologic definitions for asthma (reversible airflow limitation and airway hyperre-

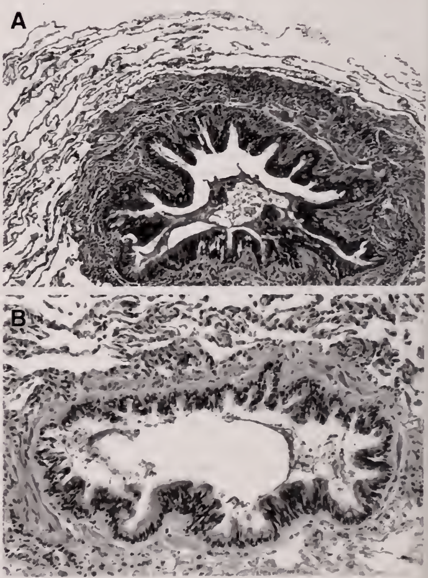

Figure Small airway from a subject who died of severe asthma (A) and a normal subject (B). Note the thickened wall, increase in inflammatory cells, constriction and mucus plugging in the severe asthmatic. (Hematoxylin and eosin stain, 20× magnification) sponsiveness) and, therefore, be confused with asthma. The observation that not all severe asthmatics have continued eosinophilic inflammation, but rather have neutrophil predominance or little inflammation, supports the theory that at least a subgroup of "severe asthmatics" may have a different disease (25, 39, 40). Interestingly, in a recent study of computed tomography (CT) scans for patients with severe asthma vs bronchiolitis obliterans (BO), another disease with severe airflow limitation, there were no changes on CT that were convincingly discriminating for BO vs asthma (41). Whether other, less well-defined obstructive diseases could also masquerade as severe asthma requires further study.

Treatment

Treatment of severe asthma remains highly problematic. Steroids remain the drug of choice, probably because of their broad and nonspecific effects. If a patient has not been on high-potency inhaled steroids, then a trial is certainly warranted (42). Whether the addition of an inhaled steroid with better peripheral distribution will reduce inflammation in the distal lung and thereby reduce severity, is not yet clear. Benefit may be seen in some cases with leukotriene modifiers, especially since a large percentage of severe asthmatics may be aspirin-sensitive (43). Long-acting beta agonists, which have efficacy in moderate, persistent asthma, do not appear to be as helpful for patients with severe disease (44, 45). In clinical trials, anti-immunoglobulin E (IgE) reduces length of hospitalization of patients with more severe forms of allergic asthma (46). Other forms of therapy, such as cyclosporin and methotrexate, have only limited applicability for this population. Prevention will remain problematic until the predisposing factors to severe asthma are better understood. However, a recent follow-up study of children with chronic lung disease of infancy suggested that prevention of certain viral infections, such as respiratory syncytial virus, with immunoglobulin preparations enhanced for antibodies against that virus, may improve long-term respiratory and allergic outcomes (15).

Conclusions

Severe asthma probably represents a heterogenous group of syndromes, including those with continued Th-2 type inflammation and those without evidence for this process. It is unlikely that appropriate treatment for the different syndromes will be similar. Therefore, it is imperative to better identify specific phenotypes of severe asthma clinically, pathologically and perhaps genetically. Approaches to treatment based on these phenotypes will be more likely to be successful.

References

1. [Wenzel SE, Fahy JV, Irvin CG, et al.] Proceedings of the ATS Workshop on Refractory Asthma — Current understanding, recommendations and unanswered questions. Am J Respir Crit Care Med 2000; 162:2341–2351.
2. Hayden ML, Dolan CM, Johnson C, et al. High level health care utilization in severe and difficult-to-treat asthma. J Allergy Clin Immunol 2002; 109:S293.
3. Oswald H, Phelan PD, Lanigan A, et al. Childhood asthma and lung function in mid-adult life. Pediatr Pulmonol 1997; 23:14–20.
4. Ulrik CS, Lange P. Decline of lung function in adults with bronchial asthma. Am J Respir Crit Care Med 1994; 150:629–634.
5. ten Brinke A, van Dissel JT, Sterk PJ, et al. Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of Chlamydia pneumoniae infection. J Allergy Clin Immunol 2001; 107:449–454.
6. Gibbs R, Miranda C, Wenzel S. Initial demographic information from an extensive data base of severe, steroid dependent asthmatics studied at National Jewish [abstract]. Am J Respir Crit Care Med 2002; 165:A119.
7. Sandford AJ, Chagani T, Zhu S, et al. Polymorphisms in the IL4, IL4RA, and FCERIB genes and asthma severity. J Allergy Clin Immunol 2000; 106:135–140.
8. Burchard EG, Silverman EK, Rosenwasser LJ, et al. Association between a sequence variant in the IL-4 gene promoter and FEV(1) in asthma. Am J Respir Crit Care Med 1999; 160:919–922.
9. Pulleyn LJ, Newton R, Adcock IM, Barnes PJ. TGFbeta1 allele association with asthma severity. Hum Genet 2001; 109:623–627.
10. Szalai C, Kozma GT, Nagy A, et al. Polymorphism in the gene regulatory region of MCP-1 is associated with asthma susceptibility and severity. J Allergy Clin Immunol 2001; 108:375–381:
11. Squillace SP, Sporik RB, Rakes G, et al. Sensitization to dust mites as a dominant risk factor for asthma among adolescents living in central Virginia. Multiple regression analysis of a population-based study. Am J Respir Crit Care Med 1997; 156:1760–1764.
12. Halonen M, Stern DA, Wright AL, et al. Alternaria as a major allergen for asthma in children raised in a desert environment. Am J Respir Crit Care Med 1997; 155:1356–1361.
13. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997; 336:1356–1363.
14. Siroux V, Pin I, Oryszczyn MP, et al. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. Eur Respir J 2000; 15:470–477.
15. Wenzel SE, Gibbs RL, Lehr MV, Simoes EA. Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. Am J Med 2002; 112:627–633.

16. Weiss ST, Tager IB, Speizer FE, Rosner B. Persistent wheeze. Its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children. Am Rev Respir Dis 1980; 122:697–707.
17. Milgrom H, Bender B, Ackerson L, et al. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 1996; 98:1051–1057.
18. Ogirala RG, Sturm TM, Aldrich TK, et al. Single, high-dose intramuscular triamcinolone acetonide versus weekly oral methotrexate in life-threatening asthma: a double-blind study. Am J Respir Crit Care Med 1995; 152:1461–1466.
19. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. Chest 1998; 113:272–277.
20. Weiss ST, Van Natta ML, Zeiger RS. Relationship between increased airway responsiveness and asthma severity in the childhood asthma management program. Am J Respir Crit Care Med 2000; 162:50–56.
21. Chan MT, Leung DY, Szefler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. J Allergy Clin Immunol 1998; 101:594–601.
22. Woolcock AJ, Rebuck AS, Cade JF, Read J. Lung volume changes in asthma measured concurrently by two methods. Am Rev Respir Dis 1971; 104:703–709.
23. Woolcock AJ, Read J. The static elastic properties in the lungs in asthma. Am Rev Respir Dis 1968; 98:788–794.
24. Gelb AF, Zamel N. Unsuspected pseudophysiologic emphysema in chronic persistent asthma. Am J Respir Crit Care Med 2000; 162:1778–1782.
25. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 1999; 160:1001–1008.
26. Kam JC, Szefler SJ, Surs W, et al. Combination IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. J Immunol 1993; 151:3460–3466.
27. Lane SJ, Adcock IM, Richards D, et al. Corticosteroid-resistant bronchial asthma is associated with increased c-fos expression in monocytes and T lymphocytes. J Clin Invest 1998; 102:2156–2164.
28. Leung DY, Hamid Q, Vottero A, et al. Association of glucocorticoid insensitivity with increased expression of glucocorticoid receptor beta. J Exp Med 1997; 186:1567–1574.
29. Takeyama K, Fahy JV, Nadel JA. Relationship of epidermal growth factor receptors to goblet cell production in human bronchi. Am J Respir Crit Care Med 2001; 163:511–516.
30. Howat WJ, Holgate ST, Lackie PM. TGF-beta isoform release and activation during in vitro bronchial epithelial wound repair. Am J Physiol Lung Cell Mol Physiol 2002; 282:L115–L123.
31. James AL, Pare PD, Hogg JC. The mechanics of airway narrowing in asthma. Am Rev Respir Dis 1989; 139:242–246.
32. Vignola AM, Riccobono L, Mirabella A, et al. Sputum metalloproteinase-9/tissue inhibitor of metalloproteinase-1 ratio correlates with airflow obstruction in asthma and chronic bronchitis. Am J Respir Crit Care Med 1998; 158:1945–1950.
33. Lemjabbar H, Gosset P, Lamblin C, et al. Contribution of 92 kDa gelatinase/type IV collagenase in bronchial inflammation during status asthmaticus. Am J Respir Crit Care Med 1999; 159:1298–1307.
34. Carroll N, Elliot J, Morton AR, James AL. The structure of large and small airways in nonfatal and fatal asthma. Am Rev Respir Dis 1993; 147:405–410.
35. Carroll NG, Mutavdzic S, James AL. Distribution and degranulation of airway mast cells in normal and asthmatic subjects. Eur Respir J 2002; 19:879–885.
36. Kraft M, Djukanovic R, Wilson S, et al. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med 1996; 154:1505–1510.
37. Balzar S, Wenzel SE, Chu HW. Transbronchial biopsy as a tool to evaluate small airways in asthma. Eur Respir J 2002 (In Press);
38. Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. Eur Respir J 1998; 12:1346–1353.
39. Wenzel SE, Szefler SJ, Leung DYM, et al. Bronchoscopic evaluation of severe asthma: Persistent inflammation associated with high dose glucocorticoids. Am J Respir Crit Care Med 1997; 156:737–743.
40. Louis R, Lau LCK, Bron AO, et al. The relationship between airways inflammation and asthma severity. Am J Respir Crit Care Med 2000; 161:9–16.
41. Jensen SP, Lynch DA, Brown KK, et al. High-resolution CT features of severe asthma and bronchiolitis obliterans. Radiology 2000; 217 Supp:595.
42. Wenzel SE, Morgan K, Griffin R, et al. Improvement in health care utilization and pulmonary function with fluticasone propionate in patients with steroid-dependent asthma at a National Asthma Referral Center. J Asthma 2001; 38:405–412.
43. Virchow Jr JC, Prasse A, Naya I, et al. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. Am J Respir Crit Care Med 2000; 162:578–585.
44. Guyer B, Gibbs R, Feldsien D Wenzel S. A pilot study to evaluate the bronchodilator response pattern to salmeterol in refractory asthma. J Allergy Clin Immunol 2002; 109:S244.
45. Nightingale JA, Rogers DF, Barnes PJ. Comparison of the effects of salmeterol and formoterol in patients with severe asthma. Chest 2002; 121:1401–1406.
46. Holgate S, Bousquet J, Wenzel S, et al. Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. Cur Med Res Opin 2001; 17:233–240.

Acronyms

BO = bronchiolitis obliterans
CS = corticosteroids
GERD = gastroesophageal reflux disease
GR = glucocorticoid receptor
MCP = monocyte chemotactic protein
SBM = subbasement membrane
TGF = transforming growth factor

Immunologic Factors in Transplant Arteriopathy:

Insight from Animal Models

Jeffrey D. Alexis, M.D., Robert T. Pyo, M.D., and Igor Chereshnev, M.D.

Abstract

Transplant arteriopathy is the leading cause of long-term morbidity and mortality following heart transplantation. The pathologic hallmark of this disease is intimal proliferation. Animal models have demonstrated that immunologic factors, including cytokines, cellular adhesion molecules and inflammatory cells, play a significant role in the development of this arteriopathy. One goal of future studies will be to translate findings in animal models into effective treatments in humans.

Key Words: Transplantation, arteriopathy, intimal proliferation, immune system, cytokine, chemokine.

Although graft rejection and infections are the major causes of mortality soon after cardiac transplant, arteriopathy is the leading cause of long-term morbidity and mortality (1). Within 5 years of cardiac transplantation, 50% of patients develop arteriopathy (2–5). Arteriopathy is also present in other organ transplants, including renal and lung transplantation. The immune system plays a key role in the development of transplant arteriopathy.

The immune system is a complex array of defenses that protect the body from foreign substances. Within the immune system there are two responses to foreign substances, the innate (natural) immune response and the acquired (adaptive) immune response (6). The extent of the acquired response increases upon repeated exposure to antigen, whereas the extent of the innate response does not change upon repeated exposure to antigen (6). The innate immune response consists of phagocytic cells (macrophages, monocytes, neutrophils), cells that mediate the release of chemical messengers (basophils, mast cells), and natural killer cells (6). The acquired immune response consists of B and T lymphocytes. B cells produce antibodies against antigens. These antibodies are either secreted or remain attached to the B cell surface (7). There are two types of T cells, cytotoxic T cells and helper T cells. Cytotoxic T cells when activated can directly kill virally infected cells (7). Most cytotoxic T cells display an antigen called CD8. Helper T cells release inflammatory mediators (cytokines) that can stimulate other cells, including cytotoxic T cells and B cells (7). Most helper T cells display CD4. Helper T cells differ in the cytokines they release. Helper T cells that release IL-2 (interleukin 2) and IFN-γ (interferon gamma) are termed Th1 cells, whereas T cells that secrete IL 4, 5, and 6 are termed Th 2 cells (6). Th1 cells are mainly involved in the activation of macrophages and cytotoxic T cells (cell-mediated immunity), whereas Th2 cells are mainly involved in the production of antibody by B cells (humoral immunity) (6).

Lymphocytes are activated when they recognize antigen. Antigen is displayed to lymphocytes by special cells called antigen presenting cells (APC). Macrophages and dendritic cells are examples of APCs (6, 7). Antigen presenting cells ingest foreign proteins (antigen), and

---

From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Jeffrey Alexis, M.D., Department of Medicine, Box 1030, Mount Sinai School of Medicine, New York, NY 10029; e-mail: jeffrey.alexis@mssm.edu

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on February 15, 2000 and updated as of October 2002.

then process the antigen as a peptide (6–8). The peptide is then "presented" by molecules called the major histocompatibility complex (MHC) (6–8). There are two types of MHC molecules, class I and class II. Class I MHC molecules are expressed on almost all somatic cells, whereas class II molecules are expressed on only certain cells, including B lymphocytes, some monocytes, and activated T cells (8). Cytotoxic T cells recognize antigen presented by class I MHC molecules and MHC class II molecules present antigen to the T cell receptor on the surface of helper T cells (Fig. 1) (6, 7). The innate and acquired immune responses work together in defending the body from foreign proteins.

Animal models have been helpful in our understanding of transplant arteriopathy and have been used to study the immunologic basis of the arteriopathy. The pathologic hallmark of this arteriopathy is intimal proliferation. Cardiac as well as arterial transplants in several species, mainly mice and rats, have been used as models of transplant arteriopathy. In animal models, if transplants are performed between animals of different strains (allogeneic transplant) arteriopathy develops, but if transplants are performed between animals of the same strain (syngeneic transplant) arteriopathy does not develop. When cardiac or arterial transplants are performed between animals of different strains (with differing MHC molecules), intimal proliferation is seen by four weeks (9–11). The earliest lesions consist of inflammatory cells, whereas later lesions consist of α-actin staining cells which may be derived from smooth muscle cells of the arterial wall or from the recipient's bone marrow (12).

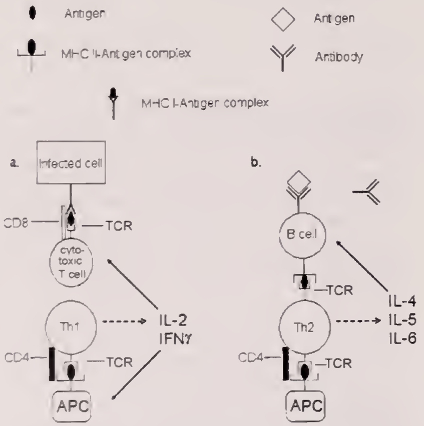

Fig. 1. Immune response to intracellular pathogens (**1a**) and extracellular pathogens (**1b**). In response to an intracellular pathogen such as a virus, an infected antigen presenting cell (e.g., macrophage) processes viral antigens as a peptide which is presented by MHC class II molecules. Th1 CD4+ helper T cell receptor (TCR) recognizes antigen presented by the MHC class II molecules and the Th1 cell secretes cytokines such as IFN-γ and IL-2 which activate CD8+ cytotoxic T cells to kill infected cells and activate macrophages to kill infected cells. In response to extracellular pathogens such as bacteria, an antigen presenting cell processes bacterial antigens and Th2 CD4+ helper T cells recognize antigen presented by MHC II molecules and secrete cytokines including Il-4, Il-5 and Il-6, which activate B cells to secrete antibodies which then neutralize or eliminate antigen. Derived from Delves PJ, Roitt IM. The immune sytem: second of two parts. N Engl J Med 2000; 343: 108–117(7).

In the cardiac transplant model, an abdominal heterotopic transplant is performed. Anastomoses are made between the aorta of the donor organ and the abdominal aorta of the recipient animal, and between the pulmonary artery of the donor organ and the inferior vena cava of the recipient animal (the recipient's heart remains in situ and functional). If cardiac transplantation is done across a full MHC mismatch (e.g. BALB/c strain mouse to C57BL/6 strain mouse), then immunosuppression with agents such as cyclosporine is required to inhibit myocardial rejection. If cardiac transplantation is done across only a class II MHC mismatch (e.g., bm12 to C57BL/6), immunosuppression is not required to inhibit rejection within the first week.

In arterial transplants, a donor arterial segment (aorta or carotid artery) is anastomosed to the recipient artery (aorta or carotid artery) in either an end-to-end anastomosis or an end-to-side anastomosis (a loop). Cardiac transplants in mice and rats have the advantage of being similar to human transplants in that the heart itself is transplanted. However, the small size of their coronary arteries limits tissue analysis, and the physiology of a heterotopic position of the transplant is different than that of a human orthotopic transplant. Aortic transplants offer the advantage of more tissue for analysis and are likely to allow for non-invasive imaging with techniques such as MRI. In addition, aortic transplants do not require immunosuppression to prevent acute rejection. Transplants in rats offer the advantage of more tissue for analysis and are technically easier than transplants in mice, whereas transplants in mice offer the advantage of using genetically altered animals.

Koulack et al. were the first to describe a method of mouse aortic transplantation in which a segment of thoracic aorta from a mouse of one strain was anastomosed to the infrarenal abdominal aorta of a mouse of a different strain (13). Two clamps were placed on the aorta of the recipient animal, and the aorta was transected between the clamps. The donor aorta was then attached end-to-end to the two ends of the transected recipient aorta, and the clamps were removed to restore blood flow. Animals sacrificed 2 months after transplant displayed intimal proliferation. Because of the small size of the vessels, thrombosis was a common problem and the most common cause of death of the recipient (74% transplantation success rate). Anesthesia, bleeding, and sepsis were other causes of death. In attempts to limit thrombosis, others have developed modifications of this technique including transplant of thoracic aorta to abdominal aorta with end-to-side anastomosis (14). We perform a thoracic aorta to abdominal aorta transplant with end-to-end anastomosis using C57BL/6 animals as donors and BALB/c mice as recipients. After the anastomosis is completed, the animals are treated with IV heparin (3.5 U per 25 g via IVC) and the clamps are released. With this approach we have achieved a 90% transplant success record (aorta remains patent without thrombosis). Like other models of transplantation, intimal proliferation is seen eight weeks after transplant (Fig. 2A). When transplantation is done between two animals of the same strain (syngeneic transplant), no intimal proliferation is seen (Fig. 2B). This helps confirm the important role of immunologic factors in the development of transplant arteriopathy.

Shi et al. demonstrated an immunologic basis of transplant arteriopathy using a carotid artery allogeneic transplant model (15). Carotid arteries from B10.A (2R) strain mice were transplanted, with end-to-end anastomoses, to recipient carotid arteries. Seven mutant mouse strains with immunologic defects, including *RAG-2* $^{-/-}$, were used as recipients. *RAG-2* (recombination-activating gene) and *RAG-1* regulate the diversity of antigen receptors (6, 16). Lymphocyte receptor genes contain four different segments (V-variable, D-diversity, J-joining, C-constant) (6). Each lymphocyte uses a different combination of genes from the V, D and J segments (one gene from each segment) to form the genetic code of its antigen receptor (6). *RAG-1*and *RAG-2* encode two of the enzymes that mediate this recombination (6). Lack of *RAG-1* or *RAG-2* interferes with lymphopoiesis, and animals that lack *RAG-1* or *RAG-2* do not have mature lymphocytes (17, 18). The 6 other mutant strains used as recipients were: *μMT* $^{-/-}$ (B cells depleted and humoral immune response deficient), *CD4* $^{-/-}$ (CD 4+ T cells absent), *MHC II* $^{-/-}$ (CD4+ T cells depleted), *MHC I* $^{-/-}$ (CD8+ T cells depleted), bg^{j}/bg^{j} (natural killer cells depleted), and op/op (macrophage colony stimulating factor and macrophages depleted). There was no difference in neointimal proliferation between the *MHC I* $^{-/-}$ recipients and *MHC I* $^{+/+}$ recipient controls, and there was no difference in neointimal proliferation between the bg^{j}/bg^{j} recipients and controls. However, in the 5 other mutant strains there were significant reductions in intimal proliferation. In *RAG-2* $^{-/-}$ mice there was almost no neointimal formation. These results showed that transplant arteriopathy is dependent on acquired immunity and requires mature CD4+ T cells, B cells, and macrophages (15).

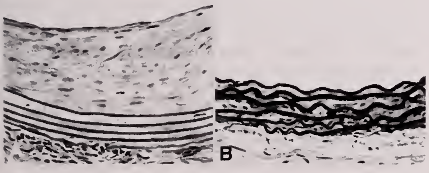

Fig. 2. Pathological analysis of aortas eight weeks following aortic transplant (Combined Masson's trichrome-elastic stain). **(A)** Aorta transplanted from C57BL/6 donor to BALB/c recipient reveals intimal proliferation (magnification, ×20). **(B)** Syngeneic transplant from BALB/c donor to BALB/c recipient does not develop arteriopathy (magnification, ×20).

Because of the important role of inflammatory cells in the development of transplant arteriopathy, research has focused on the recruitment and activation of leukocytes following transplantation. This process is regulated by chemokines, which are chemotactic cytokines. Chemokines are secreted at sites of inflammation and infection by local tissue cells, resident and recruited leukocytes and cytokine-activated endothelial cells (19). During leukocyte activation, leukocytes roll along the vessel wall, forming loose adhesions with molecules known as selectins. While rolling along the vascular wall, leukocytes come into contact with chemokines retained on cell-surface heparin sulfate proteoglycans. The chemokines activate leukocyte integrins, resulting in firmer leukocyte adhesion with the endothelium via binding between integrins on the leukocyte surface and vascular adhesion molecules such as intracellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) (19, 20). The leukocytes then migrate through tight junctions in the endothelium in response to a chemokine gradient at the site of injury.

Genetically altered mice have been used to assess the role of cytokines, selectins, vascular adhesion molecules and chemokines in the development of transplant arteriopathy (see Table). Nagano et al. demonstrated the key role that IFN-γ, a cytokine that induces chemokine production, plays in the development of this arteriopathy (21). Using a mouse heart transplant model, they transplanted hearts from the bm12 strain of mice into the C57BL/6 strain of mice (wild type and *IFN-γ* $^{-/-}$). Arteriopathy developed in wild-type recipients, but no arteriopathy developed in the *IFN-γ* $^{-/-}$ mice. Complementary to this finding were studies examining STAT (signal transducer and activator of transduction) protein families and transplant arteriopathy. STAT proteins are cytoplasmic proteins that play a key role in cell signaling (22). Upon activation (via phosphorylation), STAT proteins are translocated to the nucleus where they stimulate transcription (22). Two members of the STAT family, STAT4 and STAT6, regulate the differentiation of T lymphocytes into Th1 and Th2 cells (23). Th1 lymphocytes and Th2 lymphocytes differ in their cytokines, adhesion mechanisms and character of local response (23–27). IFN-γ is a Th1 cytokine, and STAT4 regulates IL-12 mediated Th1 differentiation (23, 28, 29) (STAT6 regulates Th2 differentiation [23, 30–32]). Koglin et al. assessed the development of transplant arteriopathy in STAT4 and STAT6 deficient mice (23). Compared with wild-type recipients, attenuated transplant arteriopathy was seen in hearts transplanted from CBA/CaJ strain mice into *STAT4* $^{-/-}$ mice (C57BL/6 background). Analyses using immunohistochemistry and reverse transcription (RT)-PCR revealed reduced graft expression of the Th1 cytokines IFN-γ and IL-2. No reduction in vasculopathy was seen in *STAT6* $^{-/-}$ recipients. This confirmed the important role of Th1 cytokines, including IFN-γ, in mediating transplant arteriopathy.

ICAM also appears to play an important role in the development of transplant arteriopathy. In a study by Shi et al., carotid arteries from *ICAM* $^{-/-}$ mice (C57BL/6 background) were transplanted into CBA/CaJ mice (33). At 42 days, there was a 52% reduction in neointimal formation in *ICAM* $^{-/-}$ donor arteries compared with controls. Similarly, using a common carotid artery (or aorta) end-to-end anastomosis to carotid artery model (C57BL/6 as donors, BALB/c as recipients), Dietrich et al. reported a 50–60% reduction in intimal proliferation in ICAM-deficient donor arteries compared with controls (animals were sacrificed at 4 weeks or 6 weeks after transplant) (34).

Unlike ICAM, the absence of P-selectin does not appear to affect the development of transplant arteriopathy (33). Using a carotid artery loop model, carotid arteries from *P-selectin* $^{-/-}$ mice (129 Sv background) were transplanted into CBA/CaJ mice. Recipients were sacrificed at 42 days. There was no difference in neointimal proliferation between P selectin $^{-/-}$ and control donor arteries.

Studies of chemokines and chemokine receptors in transplant models have focused on acute rejection as well as transplant arteriopathy. In a mouse cardiac transplant model, CCR-1 (a chemokine receptor with several chemokine ligands, including MIP1-macrophage inflammatory protein 1) was shown to play a role in both acute rejection and transplant arteriopathy (35). CCR1 animals were of the C57BL/6 background, and *CCR 1* $^{-/-}$ and *CCR 1* $^{+/+}$ animals were used as recipients. No immunosuppression was used. When BALB/c mice were used as donors (full MHC mismatch), there was increased survival of the graft in *CCR 1* $^{-/-}$ recipients compared with *CCR 1* $^{+/+}$ recipients (13.5±0.9 days vs. 7.4±0.8 days). When bm12 mice were used as donors to *CCR 1* $^{+/+}$ mice (class II mismatch), the donor graft survived 33.4±1.9 days. However, when bm12 mouse hearts were transplanted into *CCR 1* $^{-/-}$ recipients, the grafted hearts survived more than 100 days, and at 100 days no transplant arteriopathy was seen. Thus, absence of CCR 1 inhibited both acute rejection and transplant arteriopathy. In an analogous study of the chemokine receptor CCR 5 (a chemokine receptor with several chemokine ligands including MIP1), transplantation of bm12 mouse hearts into *CCR 5* $^{-/-}$ mice (C57BL/6 background) resulted in permanent graft survival (more than 100 days) and inhibition of arteriopathy (36).

These animal studies have established several important components of the immune response as likely contributors to the development of transplant arteriopathy (Table). Goals of future studies will be to better understand the etiology of the disease and to translate findings in animal models into effective treatments in humans. One such treatment may utilize the im-

TABLE

Studies of Cytokines, Selectins, Adhesion Molecules and Chemokines in Transplant Arteriopathy

Study	**Mouse Model**	**Mice Strains Donor→ Recipient**	**Result (knockout mouse compared with control*)**
γ-IFN[21]	Cardiac transplant	bm12→ C57BL/6	Total inhibition of arteriopathy
STAT 4[23]	Cardiac transplant	CBA/CaJ→ C57BL/6	36% reduction in luminal occlusion
ICAM[33]	Carotid loop transplant	C57BL/6→ CBA/CaJ	52% reduction in neointimal formation
ICAM[34]	Arterial and cardiac transplant	C57BL/6→ BALB/c	50–60% reduction in neointimal formation
P Selectin[33]	Carotid loop transplant	129 Sv→ CBA/CaJ	No reduction in neointimal formation
CCR-1[35]	Cardiac transplant	bm12→ C57BL/6	Total inhibition of arteriopathy
CCR-5[36]	Cardiac transplant	bm12→ C57BL/6	Total inhibition of arteriopathy

*knockout mice and wild type controls are of C57BL/6 background except in P selectin study, where knockout mice and wild type controls are of 129 Sv background.

munosuppressant Rapamycin, which has been shown to decrease intimal proliferation in animal studies (37–40) and is now being studied in humans. Thus, further studies of immunologic factors in transplant arteriopathy may greatly aid in developing effective treatments for this disease.

Conclusion

Transplant arteriopathy is the major cause of long-term morbidity and mortality following heart transplantation. Animal models have demonstrated that immunological factors play a key role in the development of the disease. Future studies will try to elucidate the pathogenesis of the disease and find effective treatments to reduce or eliminate transplant arteriopathy.

Acknowledgments

The authors thank Dr. Mark Taubman for his help in reviewing the manuscript, and Dr. John Fallon, Otis DeFreitas, and Yolanda Ortega for their assistance with histopathology.

References

1. Sarris GE, Moore KA, Schroeder JS, et al. Cardiac transplantation: the Stanford experience in the cyclosporine era. J Thorac Cardiovasc Surg 1994; 108:240–251; discussion 251–252.
2. Schroeder JS, Gao SZ, Alderman EL, et al. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. N Engl J Med 1993; 328: 164–170.
3. Gao SZ, Schroeder JS, Alderman EL, et al. Clinical and laboratory correlates of accelerated coronary artery disease in the cardiac transplant patient. Circulation 1987; 76:V56–V61.
4. Uretsky BF, Murali S, Reddy PS, et al. Development of coronary artery disease in cardiac transplant patients receiving immunosuppressive therapy with cyclosporine and prednisone. Circulation 1987; 76:827–834.
5. Gao SZ, Schroeder JS, Alderman EL, et al. Prevalence of accelerated coronary artery disease in heart transplant survivors: comparison of cyclosporine and azathioprine regimens. Circulation 1989; 80:111100-111105.
6. Delves PJ, Roitt IM. The immune system: first of two parts. N Engl J Med 2000; 343:37–49.
7. Delves PJ, Roitt IM. The immune system: second of two parts. N Engl J Med 2000; 343:108–117.
8. Klein J, Sato A. The HLA system: first of two parts. N Engl J Med 2000; 343:702–709.
9. Mennander A, Tiisala S, Halttunen J, et al. Chronic rejection in rat aortic allografts: an experimental model for transplant arteriosclerosis. Arterioscler Thromb 1991; 11:671–680.
10. Geraghty JG, Stoltenberg RL, Sollinger HW, Hullett DA. Vascular smooth muscle cells and neointimal hyperplasia in chronic transplant rejection. Transplantation 1996; 62:502–509.
11. Laden AM, Sinclair RA. Thickening of arterial intima in rat cardiac allografts: a light and electron microscopic study. Am J Pathol 1971; 63:69–84.
12. Shimizu K, Sugiyama S, Aikawa M, et al. Host bone-marrow cells are a source of donor intimal smooth-muscle-like cells in murine aortic transplant arteriopathy. Nat Med 2001; 7:738–741.
13. Koulack J, McAlister VC, Giacomantonio CA, et al. Development of a mouse aortic transplant model of chronic rejection. Microsurgery 1995; 16:110–113.
14. Sun H, Valdivia LA, Subbotin V, et al. Improved surgical technique for the establishment of a murine model of aortic transplantation. Microsurgery 1998; 18:368–371.
15. Shi C, Lee WS, He Q, et al. Immunologic basis of transplant-associated arteriosclerosis. Proc Natl Acad Sci U S A 1996; 93:4051–4056.
16. Nagaoka H, Yu W, Nussenzweig MC. Regulation of RAG expression in developing lymphocytes. Curr Opin Immunol 2000; 12:187–190.
17. Mombaerts P, Iacomini J, Johnson RS, et al. RAG-1-deficient mice have no mature B and T lymphocytes. Cell 1992; 68:869–877.
18. Shinkai Y, Rathbun G, Lam KP, et al. RAG-2-deficient mice lack mature lymphocytes owing to inability to initiate V(D)J rearrangement. Cell 1992; 68:855–867.
19. Luster AD. Chemokines — chemotactic cytokines that mediate inflammation. N Engl J Med 1998; 338:436–445.
20. Herlaar E, Brown Z. p38 MAPK signalling cascades in inflammatory disease. Mol Med Today 1999; 5:439–447; http://DX.DOI.org/10.1016/51357-4310(99)01544-0

21. Nagano H, Mitchell RN, Taylor MK, et al. Interferon-gamma deficiency prevents coronary arteriosclerosis but not myocardial rejection in transplanted mouse hearts. J Clin Invest 1997; 100:550–557.
22. Darnell JE, Jr., Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science 1994; 264: 1415–1421.
23. Koglin J, Glysing-Jensen T, Gadiraju S, Russell ME. Attenuated cardiac allograft vasculopathy in mice with targeted deletion of the transcription factor STAT4. Circulation 2000; 101:1034–1039.
24. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol 1989; 7:145–173.
25. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature 1996; 383:787–793.
26. Austrup F, Vestweber D, Borges E, et al. P- and E-selectin mediate recruitment of T-helper-1 but not T-helper-2 cells into inflammed [sic] tissues. Nature 1997; 385:81–83.
27. Sallusto F, Lenig D, Mackay CR, Lanzavecchia A. Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes. J Exp Med 1998; 187: 875–883.
28. Kaplan MH, Sun YL, Hoey T, Grusby MJ. Impaired IL-12 responses and enhanced development of Th2 cells in Stat4-deficient mice. Nature 1996; 382:174–177.
29. Thierfelder WE, van Deursen JM, Yamamoto K, et al. Requirement for Stat4 in interleukin-12-mediated responses of natural killer and T cells. Nature 1996; 382:171–174.
30. Kaplan MH, Schindler U, Smiley ST, Grusby MJ. Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. Immunity 1996; 4:313–319.
31. Shimoda K, van Deursen J, Sangster MY, et al. Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. Nature 1996; 380:630–633.
32. Takeda K, Tanaka T, Shi W, et al. Essential role of Stat6 in IL-4 signalling. Nature 1996; 380:627–630.
33. Shi C, Feinberg MW, Zhang D, et al. Donor MHC and adhesion molecules in transplant arteriosclerosis. J Clin Invest 1999; 103:469–474.
34. Dietrich H, Hu Y, Zou Y, et al. Mouse model of transplant arteriosclerosis: role of intercellular adhesion molecule-1. Arterioscler Thromb Vasc Biol 2000; 20:343–352.
35. Gao W, Topham PS, King JA, et al. Targeting of the chemokine receptor CCR1 suppresses development of acute and chronic cardiac allograft rejection. J Clin Invest 2000; 105:35–44.
36. Gao W, Faia KL, Csizmadia V, et al. Beneficial effects of targeting CCR5 in allograft recipients. Transplantation 2001; 72:1199–1205.
37. Meiser BM, Billingham ME, Morris RE. Effects of cyclosporin, FK506, and rapamycin on graft-vessel disease. Lancet 1991; 338:1297–1298.
38. Gregory CR, Huie P, Billingham ME, Morris RE. Rapamycin inhibits arterial intimal thickening caused by both alloimmune and mechanical injury. Its effect on cellular, growth factor, and cytokine response in injured vessels. Transplantation 1993; 55:1409–1418.
39. Schmid C, Heemann U, Azuma H, Tilney NL. Rapamycin inhibits transplant vasculopathy in long-surviving rat heart allografts. Transplantation 1995; 60:729–733.
40. Goggins WC, Fisher RA, Cohen DS, et al. Effect of single-dose rapamycin-based immunosuppression on the development of cardiac allograft vasculopathy. J Heart Lung Transplant 1996; 15:790–795.

Laboratory Aspects of Tick-Borne Diseases:

Lyme, Human Granulocytic Ehrlichiosis and Babesiosis

Maria E. Aguero-Rosenfeld, M.D.

Abstract

Lyme disease, human granulocytic ehrlichiosis (HGE) and babesiosis are emerging infections in the northeastern and midwestern United States, where *Ixodes scapularis* ticks are prevalent. Lyme disease and babesiosis have also been reported on the West Coast, but less frequently. Lyme disease presents frequently with a skin lesion known as erythema migrans (EM), and diagnostic tests are not necessary if the lesion is classical. Those patients presenting without EM or with atypical skin lesions may need laboratory confirmation. The most frequently used laboratory modality consists of the 2-step serological assays, employing a sensitive ELISA as a first step, followed by IgG and/or IgM immunoblots. Current guidelines for interpretation are those recommended by the CDC. HGE and babesiosis are febrile illnesses with non-specific signs and symptoms. Both infections may present with routine laboratory abnormalities, including leukopenia and/or thrombocytopenia in HGE and anemia in babesiosis. Moderate elevations of liver enzymes may occur in all three tick-borne infections. Specific diagnostic modalities for acute-phase HGE include buffy coat smear examination, culture and PCR. Culture appears to have the greatest sensitivity of the three tests. Babesiosis can be diagnosed by peripheral blood examination for the intraerythrocytic parasites, PCR or serology. Co-infections with these agents exist, but they should be documented by detection of the organisms rather than by serology, since seroprevalence rates are high in endemic areas.

Key Words: Tick-borne diseases, Lyme disease, ehrlichiosis, babesiosis.

TICK-BORNE INFECTIOUS DISEASES are being recognized with increasing frequency in the northeastern and midwestern United States, where *Ixodes scapularis* ticks are prevalent. In these geographic areas, the white-footed mouse (*Peromyscus leucopus*) serves as the natural reservoir for *Borrelia burgdorferi*, *Anaplasma phagocytophilum* and *Babesia microti*, the agents causing Lyme disease, human granulocytic ehrlichiosis (HGE) and babesiosis, respectively (1, 2). The carriage rate of these agents by *I. scapularis* varies in different studies, and theoretically co-transmission of more than one pathogen can occur (3). In fact, tick-borne co-infections as determined by culture or other direct methods have been reported in humans (4). The most frequent developmental stage of *I. scapularis* responsible for transmission of these pathogens appears to be the nymphal stage, when, due to its small size, it is not easily detected while taking a blood meal on humans. A single dose of doxycycline has been found to prevent the transmission of *B. burgdorferi* when taken soon after the removal of an engorged nymphal tick which has been attached for more than 48 hours (5). These tick-borne diseases are also common in Europe, where they are transmitted by *Ixodes ricinus*.

Lyme Disease

Currently, Lyme disease is the most frequently transmitted vector-borne disease encountered in the United States, with approximately 16,000 cases reported each year. Although cases have been reported from most states, a majority are from southern New York State, Connecticut and the upper Midwest (6).

From the Department of Pathology, New York Medical College, Westchester Medical Center, Valhalla, NY.

Address all correspondence to Maria E. Aguero-Rosenfeld, M.D., Clinical Laboratories, Room 1J-11a, Westchester Medical Center, Valhalla, NY 10595; E-mail: <m_aguero-rosenfeld@nymc.edu>

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY, on February 12, 2002, and updated as of January 16, 2003.

Characteristics of *Borrelia burgdorferi*

B. burgdorferi is a thin, spiral, motile, extracellular bacterium belonging to the family Spirochaetaceae. Unique features of *Borrelia* are the presence of a linear chromosome and several linear and circular plasmids that encode for outer surface proteins. Of the several outer surface proteins (Osp), OspA and OspC are of diagnostic and pathogenetic importance. These Osps are differentially expressed when the organism is in the tick midgut and when it is in the mammalian host (7). While OspA is preferentially expressed on the surface of *B. burgdorferi* in the midgut of the infected unfed tick, OspC is expressed on the surface of the organism after the tick obtains a blood meal. This switch in expression appears to be mediated by factors present in blood, as well as by changes in temperature from 25 to 37°C (8). When efficient transmission of *B. burgdorferi* from the tick to the susceptible host occurs, the organisms are primarily expressing OspC on their surface; this explains the importance of OspC as an early immunodominant antigen (9, 10). The differential expression of Osps also explains the bactericidal effect of sera from individuals who have received the vaccine containing OspA antigen. The effect of this formerly available recombinant Lyme vaccine was to prevent transmission of *B. burgdorferi* to a susceptible host by killing the organism in the midgut of the infected tick (11).

Other important antigenic structures of *B. burgdorferi* are the flagella that are encased within the outer membrane: the flagellar protein flagellin (41-kDa) is an important immunodominant antigen that elicits strong antibody response in Lyme disease patients (12). Although highly immunogenic, the 41-kDa antigen is also highly cross-reactive. Other antigens of importance are the 93-kDa (a protoplasmic protein), the Bmp family of proteins of about 39-kDa, the 37-kDa (fla A, outer sheet protein of the periplasmic flagella), among others, and a variable surface antigen of about 35-kDa (vlsE) that has been recently found to be highly antigenic and specific to *B. burgdorferi* (13–16).

Genospecies of *B. burgdorferi*

Genetic analysis of *B. burgdorferi* causing disease in North America and Europe has shown that differences exist among strains; this finding led to several nomenclature changes. Thus, *B. burgdorferi sensu lato* now includes the genospecies *B. burgdorferi sensu stricto*, which causes Lyme disease in North America and Europe; *B. garinii*, which causes more neurological disease; and *B. afzelii*, which causes chronic skin lesions. *B. garinii* and *B. afzelii* are more prevalent in Europe (17, 18).

Clinical Presentation of Lyme Disease

The disease may follow different stages after the efficient transmission of *B. burgdorferi* through the tick bite (19).

A. Early

- Erythema migrans (EM) is an expanding annular skin lesion that appears after 10–14 days at the site of the tick bite. It is believed to occur in about 90% of infected individuals, and since it may be completely asymptomatic, it may be unrecognized when present in certain areas of the body such as the back or behind the knees. When skin lesion presents with minimal symptoms or it is asymptomatic, it is referred to as early localized EM.
- Some patients present with EM, or within weeks after EM, with signs and symptoms of disseminated disease which include severe headaches, multiple skin lesions (multiple EMs), cranial palsies (Bell's palsy), and cardiac arrhythmias. This type of presentation is referred to as early disseminated disease.

B. Late

- Arthritis is most frequently caused by *B. burgdorferi sensu stricto* and appears weeks to months after untreated early Lyme disease. It is the most frequent late manifestation in North America and the one that led to the description of the disease by Steere and colleagues in the late 1970s (20, 21).
- Achrodermatitis chronica atrophicans (ACA) is the late manifestation associated with *B. afzelii* in Europe.
- Chronic neurological manifestations such as encephalopathy have also been associated with late Lyme disease, particularly in Europe.

Diagnosis of Lyme Disease

A. Clinical: Characteristic expanding annular lesion at the port of entry (EM) of more than 5 cm diameter is the hallmark of early disease. The presence of this lesion is sufficient to make the diagnosis of early Lyme disease, and laboratory tests are not necessary to confirm the diagnosis. Problems arise when the skin lesion is unnoticed or is atypical, or when patients present after EM has disappeared. Laboratory tests may be of assistance in these situations.

B. Laboratory tests for detection of B. burgdorferi

1. Direct methods

- **Microscopy**: The organism can be visualized by fluorescent antibody or silver staining methods. The best yield has been achieved from skin biopsies obtained from the EM lesion (22, 23). The presence of spirochetes in skin lesions from patients with ACA had been reported long before Lyme disease was described in the United States.
- **Polymerase chain reaction (PCR)** has also been used to detect *B. burgdorferi* nucleic acids in different clinical specimens. Again, the best yield has been obtained from skin specimens from EM lesions with sensitivities exceeding 80% (24, 25). Although testing of cerebrospinal fluid, blood and urine has been done with variable degrees of sensitivity, the best use of this method appears to be for the testing of synovial fluid. In a study of 90 samples of synovial fluid collected during a 17-year period from different patients with Lyme arthritis, using primer sets to amplify the flagellin gene, as well as OspA primers, PCR was more frequently positive for those patients with untreated or partially treated arthritis than for those patients treated for prolonged periods of time (26).
- **Culture:** *B. burgdorferi* can be cultured *in vitro* in BSK (Barbour, Stoenner and Kelly) medium after days or weeks of incubation (27). The organism can be isolated in culture from skin lesions as well as from blood (28, 29). The yield of recovery from blood is about 50% when volumes of blood of at least 18 mL are cultured (30). Wormser et al. (31) found that the yield of recovery was associated with the type of organism involved in the infection, as determined by a PCR-restriction fragment length polymorphism (RFLP) typing scheme. Type 1 *B. burgdorferi* strains were more frequently associated with early-disseminated disease and were more frequently cultured from blood specimens.

2. Antibody methods

Due to the cumbersome nature of culture methods and the availability of PCR technology in only a few centers and reference laboratories, antibody testing is the most frequent laboratory modality used to assist in the diagnosis of Lyme disease. Different formats have been available since the initial description of Lyme disease, including indirect fluorescent antibody assay (IFA), enzyme-linked immunosorbent assay (ELISA) and Western immunoblots. Earlier methods included antigen preparations of *B. burgdorferi* highly passed in culture, which we now know were devoid of important immunodominant antigens such as OspC (32).

Since *B. burgdorferi* shares some antigens with other bacteria, especially other spirochetes, antibody methods using whole-cell *B. burgdorferi* as a source of antigen are likely to also detect non-specific antibodies. In 1994, the Centers for Disease Control and Prevention (CDC) and other agencies co-sponsored a conference to standardize *B. burgdorferi* antibody testing. Among the recommendations from this meeting was the use of 2-step testing for *B. burgdorferi* antibodies. The first step should include a sensitive enzyme immunoassay or IFA followed by the second step consisting of Western immunoblots for those testing reactive by the first step. This first step should detect both IgG and IgM antibodies to *B. burgdorferi*. Furthermore, it was recommended that during the first 4 weeks after onset of disease, both IgG and IgM immunoblots should be performed. For patients with disease of more than one month duration, only IgG blot should be performed (33).

3. Criteria for immunoblot interpretation

- Positive IgM blot: presence of 2 of 3 significant bands: 23-kDa (OspC), 39 and 41-kDa
- Positive IgG blot: presence of 5 of 10 significant bands: 18-kDa, OspC, 28, 30, 39, 41, 45, 58, 66 and 93-kDa

Although not without limitations, 2-step testing has been an important advance in the standardization of *B. burgdorferi* serology. Enzyme immunoassays (EIA) are quite amenable to automation and quantification of antibodies present. More than 40 commercially available first-step test kits are currently being used. For the most part, they are quite comparable in the detection of IgG antibodies, but they have variable degrees of sensitivity in the detection of IgM antibodies. Immunoblots suffer from the subjectivity of band scoring. At this writing, three commercially available immunoblot kits are FDA approved.

4. Characteristics of **B. burgdorferi** *serology, using the 2-step approach*

- Most patients with early disease fulfill criteria for positivity, with strong IgM reactivity to OspC in immunoblots.
- Seroconversion usually occurs within 2 weeks of onset of disease, with or without the use of antimicrobial therapy (14).
- Patients with early-disseminated disease develop higher antibody response to *B. burgdorferi* than those patients with early-localized disease (14).
- Patients with late disease are usually seropositive at the time of presentation and develop high-titer antibodies as determined by high ratios or indices on EIA. They also display many immunoreactive bands in IgG immunoblots (13).
- Patients developing high antibody titers remain positive for prolonged periods of time, sometimes years, after successful antimicrobial treatment. Therefore, antibody testing should not be used to follow the response to treatment.
- Individuals who received the recombinant OspA Lyme vaccine react positive in the first step, but the blot reactivity is different from that observed after the natural infection and will not be interpreted as positive by the second step (34). However, since the manufacturer (SmithKline Beecham, Philadelphia, PA), has withdrawn the vaccine (LIMErix) from the market, the effects of vaccination on *B. burgdorferi* serology will not be an issue any longer.

5. Other antibody methods

- While searching for a specific antigen of *B. burgdorferi*, researchers identified a variable antigen (vlsE) with potential use in EIA as a single-step test. Regions of this antigen are conserved, are quite similar for different genospecies of *B. burgdorferi sensu lato*, and are highly immunogenic, making them ideal candidates as specific antigens. One of these regions (C6 peptide) has been synthesized and used in an EIA format; it has recently been approved for use to detect *B. burgdorferi* antibodies (35). Evaluations of the C6 ELISA to determine whether it would replace the 2-step test are currently being carried out.
- Several investigators have produced recombinant *B. burgdorferi* antigens for use in EIA, blot or immunodot formats (36). Although potentially useful, they have not been broadly used. The complex antigenic composition of *B. burgdorferi sensu lato* and the variable antibody response developed by patients to these antigens limit the use of recombinant assays. Such recombinant antigens may not contain the epitopes to which patients develop antibodies. Furthermore, patent issues have limited the broad availability of these assays.
- Functional antibody assays: During active infection, patients develop borreliacidal antibodies (37). Although quite specific, these assays have limited use. The procedure involves the use of microscopy or flow cytometry to evaluate the effect of the patient's serum on live *B. burgdorferi* spirochetes. Due to its cumbersome nature, the procedure has been employed in few laboratories.

Human Granulocytic Ehrlichiosis

Human ehrlichioses are febrile illnesses recently recognized in the United States (Table). They are caused by obligate intracellular bacteria which infect different types of leukocytes and are transmitted through the bite of infected ticks. Recent reclassification, based on sequencing of genes encoding the 16S rRNA and groESL, has placed these organisms in different genera (38, 39).

The first human ehrlichiosis described in the U.S. (1986) is human monocytic ehrlichiosis (HME), caused by *Ehrlichia chaffeensis* and transmitted by *Amblyomma americanum* ticks (40). This infectious disease is prevalent in the southern and south central United States.

Human granulocytic ehrlichiosis (HGE) is caused by the recently renamed *Anaplasma phagocytophilum*, which includes the veterinary pathogens formerly known as *Ehrlichia equi* (agent of equine granulocytic ehrlichiosis) and *Ehrlichia phagocytophila* (agent of tick fever of sheep in Europe) (38, 39).

Human ehrlichiosis caused by the canine pathogen *Ehrlichia ewingii* has also been described, but mostly in immunocompromised patients. It is also transmitted through the bite of *A. americanum* and has only been reported in the same geographic areas where HME exists (41).

The first human ehrlichiosis ever described was sennetsu fever, a mononucleosis-like illness, caused by *E. sennetsu*, now renamed *Neorickettsia sennetsu*. This ehrlichiosis was first reported in patients from Japan and Malaysia in

TABLE
Human Ehrlichioses

Disease	Organism	Infected cell	Vector/Transmission	Geographic location
Human Granulocytic Ehrlichiosis (HGE)	*Anaplasma phagocytophilum*	Granulocytic leukocytes	*Ixodes scapularis*	Northeastern and midwestern United States
Human Monocytic Ehrlichiosis (HME)	*Ehrlichia chaffeensis*	Mononuclear leukocytes	*Amblyomma americanum*	South central and southern United States
E. ewingii human ehrlichiosis	*Ehrlichia ewingii* (agent of canine granulocytic ehrlichiosis)	Granulocytic leukocytes	*Amblyomma americanum*	South central and southern United States
Sennetsu fever	*Neorickettsia sennetsu*	Mononuclear leukocytes	Ingestion of infected fish?	Asia (Japan, Malaysia)

the 1950s and appears to be transmitted by ingestion of infected fish (42).

Clinical Presentation of HGE

Most HGE cases are reported between late spring and fall, and usually involve adults. Bakken et al. first described HGE in 1994 as occurring mainly in elderly men with a febrile illness, some of whom presented with severe disease (43, 44). The first described cohort of patients from our medical center presented with a milder form of the illness characterized by fever, myalgias, headache and other constitutional signs and symptoms that occurred about 5 days after the tick bite (45). Although the most frequent mechanism of acquisition is by an infected tick bite, other modes probably occur, such as perinatal transmission described in a newborn (46).

Laboratory Abnormalities

Characteristically, patients develop leukopenia with left shift, lymphopenia and thrombocytopenia during the acute phase of the disease. These hematological changes tend to normalize during the second week of illness and even before effective antimicrobial therapy is established; lymphocytosis with atypical lymphocytes may then appear (47). Moderate elevations of liver enzymes including transaminases and lactate dehydrogenase also occur during the acute phase of the illness (43–45).

Since the clinical manifestations and routine laboratory abnormalities are nonspecific, laboratory tests aimed at detecting the etiologic agent (direct tests) as well as antibodies elicited by the infection are of particular importance.

Direct Tests

During the acute phase and prior to the establishment of specific treatment, *A. phagocytophilum* can be detected by microscopy, culture or specific nucleic acid sequences amplified by polymerase chain reaction (PCR). These tests can be performed on edetic acid (EDTA)-anticoagulated blood (44, 45).

Microscopy

Since patients may be leukopenic at the time of presentation and very few leukocytes are usually infected, it is necessary to examine stained buffy coat smear preparations. Infrequently, patients present with high numbers of infected leukocytes that can be visualized on routine peripheral blood smears stained with a Romanowsky-type stain (Wright, Giemsa). Intragranulocytic inclusions (morulae) represent *A. phagocytophilum* microcolonies with hundreds or even thousands of organisms in a membrane-lined vacuole. *A. phagocytophilum* morulae stain basophilic and their stippled appearance and staining properties distinguish them from Döhle's bodies or overlying platelets (Fig. 1). Also, while several morulae may be seen in a given granulocyte, usually only a single morula is observed. Stained buffy coat smears are examined microscopically using 50× or

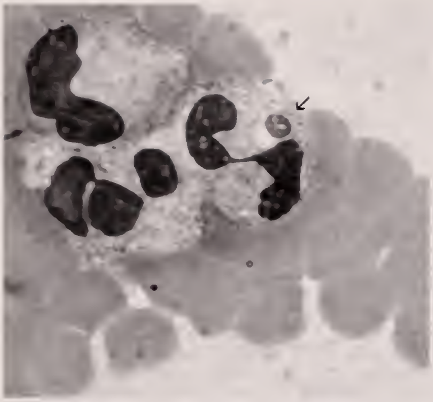

Fig. 1. Photomicrograph of a buffy coat smear preparation stained with Wright's stain showing a neutrophilic leukocyte infected with *A. phagocytophilum*. Arrow is pointing at an intragranulocytic inclusion (morula) (100× magnification).

100× magnification, and at least 800–1,000 granulocytes are examined before the smear is reported negative (44, 45). Although examination of stained buffy coat is the fastest and most inexpensive laboratory test, it is also the most insensitive. In our experience, about 60% of those patients confirmed by culture tested positive by smear during the acute phase of the illness (47).

Culture

Since *A. phagocytophilum* is an obligate intracellular bacterium with tropism for granulocytic leukocytes, it has successfully been cultured in HL-60 cells, a promyelocytic leukemia cell line. Since the first report on the culture of *A. phagocytophilum* by Goodman et al. (48), several investigators have used this modality of diagnosis. Since late 1995, more than 50 *A. phagocytophilum* isolates have been cultured from HGE patients at Westchester Medical Center (unpublished data). At our institution we culture 0.2 mL of EDTA blood into a flask containing approximately 2 × 10^5 HL-60 cells in RPMI 1640 with L-glutamine (Roswell Park Memorial Institute) medium containing 10% fetal bovine serum. Cultures are incubated at 37°C under 5% CO_2 for up to 14 days. Every 3–4 days an aliquot is removed to determine the presence of infection of HL-60 cells and to adjust the cell density. Infection of HL-60 cells is confirmed by detecting the characteristic intracytoplasmic inclusions after Wright staining of cytocentrifuged culture aliquots (Fig. 2). Most cultures yielding a positive result become positive during the first week of incubation. In our experience, culturing of *A. phagocytophilum* is the most sensitive method to confirm the diagnosis of HGE during the acute phase and prior to effective antimicrobial treatment such as doxycycline (unpublished data). Since *A. phagocytophilum* can remain viable in infected blood kept refrigerated for up to 18 days (49), refrigerated EDTA blood can be transported to a laboratory where the appropriate cultures can be carried out.

Polymerase Chain Reaction

Several primer sets have been used to amplify specific nucleic acid sequences of *A. phagocytophilum*. Among the targeted sequences are the 16S rRNA, *gro*ESL, *epank*1 and the genes encoding for the immunodominant 44-kDa antigens (44, 50–52). Of these, it appears that primers amplifying the *epank*1 and the 44-kDa antigens offer the greatest sensitivity. The *epank*1 genes encode for a highly specific protein of *A. phagocytophilum* and, as for the genes encoding the 44-kDa antigens, they are present in multiple copies in the genome.

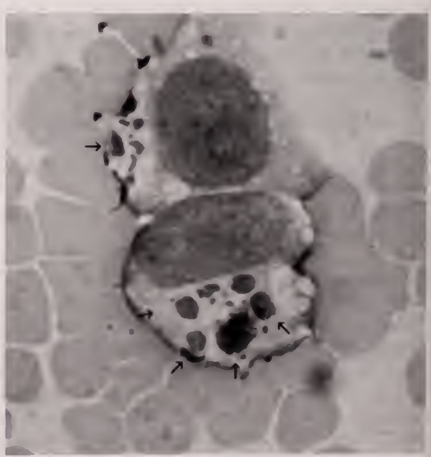

Fig. 2. Cytocentrifuged preparation of a culture of *A. phagocytophilum* in HL-60, promyelocytic leukemia cell line, stained with Wright's stain. Arrows are pointing at *A. phagocytophilum* inclusions (100× magnification).

PCR has a sensitivity of about 75–80% compared with culture during the acute phase of illness (47).

Serology

Antibodies are frequently detected by using an indirect immunofluorescent antibody assay (IFA). Earlier preparations included antigen derived from infected horse polymorphonuclear neutrophils, which were then known as *E. equi* (53). Currently human isolates are used as the source of antigen in IFA preparations (54–56). Serum specimens are tested at an initial dilution of 1/64–1/80 and those testing reactive at this dilution are tested after serial dilutions to determine the titer. Bound antibodies are detected after incubation with fluorescent anti-human IgG/IgM conjugates. Our evaluation of the serology of culture-confirmed HGE cases has shown that most patients (>95%) develop antibodies. Antibodies usually appear within 2 weeks of onset of symptoms with or without the use of antimicrobial therapy and reach levels which can be detected in serum diluted to 640 or more during the first month of illness (54). Antibodies may remain detectable for more than a year after successful antimicrobial therapy. Although it is a highly sensitive diagnostic modality, serology suffers from several limitations, including the need for acute and convalescent phase testing. Seroprevalence studies have shown that approximately 11–15% of healthy individuals living in endemic areas may have detectable antibodies by IFA (57, 58). The frequency of *A. phagocytophilum* antibodies is even higher in adult populations testing positive for antibodies to *B. burgdorferi*. Interestingly, the frequency of antibodies to *A. phagocytophilum* is only about 5% in sera from children younger than 19 years of age, regardless of the presence of *B. burgdorferi* antibodies (58). Together with the fact that few children have been diagnosed with HGE, it appears that children are less susceptible to *A. phagocytophilum* infection. The IFA titers found in sera of individuals in the seroprevalence studies referred to above, however, have been lower than 320. It appears prudent to use higher IFA cut-off titers when serology is used to confirm a recent infection.

Other antibody methods include the use of enzyme immunoassays employing purified *A. phagocytophilum* antigens or recombinant antigens (56, 59). *A. phagocytophilum* has immunodominant antigens of 42–44 kDa size encoded by a multigene family (60). They are the predominant reactive band(s) in immunoblots prepared with purified *A. phagocytophilum* (53, 55, 56).

Babesiosis

This infection is caused by intraerythrocytic parasites, with widespread distribution worldwide. They are classified in the phylum Apicomplexa, also called Sporozoa, in the order Piroplasmida, and are commonly referred to as piroplasms due to their pear shape. More than 100 species of *Babesia* have been described, infecting different vertebrate hosts. *B. microti, B. divergens* and the unnamed species WA-1, CA-1 and MO1 have been found to infect humans (61). Most infections in the United States are caused by *B. microti*, preferentially in the Northeast and Midwest, where they are transmitted by *I. scapularis* ticks. WA-1, CA-1 and MO-1 occur mostly in the West Coast of the U.S., but the vector involved in their transmission remains unknown (62). Another important mechanism of acquisition is by transfusion of blood obtained from infected individuals. Since most infections are probably asymptomatic, chronic low-level parasitemic patients may be the source of infections acquired by transfusion (63).

Clinical manifestations range from mild to severe, perhaps reflecting the degree of parasitemia. More severe presentation usually occurs in the immunocompromised, and splenectomized, and in elderly hosts. It is believed that most infections are mild and perhaps asymptomatic. More severe infections have also been reported in those patients co-infected with *B. burgdorferi* (64). Signs and symptoms of babesiosis usually include fever, malaise, fatigue, and anemia. Hepatomegalia and splenomegalia may be present. Laboratory abnormalities include anemia, leukopenia and elevation of liver enzymes.

Laboratory Diagnosis

Microscopy. Peripheral blood smears stained with Wright or Giemsa are examined under 100× oil magnification for intraerythrocytic forms. *B. microti* ring forms (merozoites) are usually small, 1.5–2.0 μm, single, paired or rarely in tetrads ("Maltese cross"); they may also be extraerythrocytic (Fig. 3).

Polymerase chain reaction. Use of this method has been proven to be more sensitive than and equally specific as microscopy for the

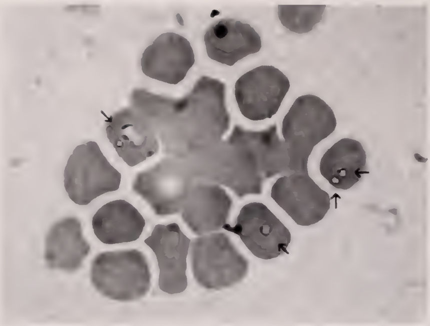

Fig. 3. Intraerythrocytic inclusions of *Babesia microti* in a Wright-stained peripheral blood smear (arrows) (100× magnification).

diagnosis of babesiosis (65). Highly conserved sequences such as a nuclear small-subunit ribosomal gene of *B. microti* (nss-rDNA) are amplified by PCR. Presence of babesial DNA correlates with active infection. The use of PCR has also contributed to the description of new babesial species (62, 66).

Serology. Antibodies are measured by an IFA using hamster-derived *B. microti* antigen. Titers higher than 128 or 256 have greater diagnostic specificity than low titers. Antibodies may remain elevated for prolonged periods of time after the acute infection.

Other modalities of laboratory diagnosis include the inoculation of patient blood into laboratory animals. EDTA-blood is inoculated intraperitoneally into hamsters. Infection in hamsters is detected by microscopic examination of Wright-stained blood smears.

Conclusion

Tick-borne infectious diseases have become an important component of the differential diagnoses of febrile illnesses occurring between spring and late fall. Unlike Lyme disease, which presents with a characteristic skin lesion, HGE and babesiosis may only present with some routine laboratory abnormalities. Co-infections have been reported, as confirmed by simultaneous detection of the etiologic agents. Caution should be exercised when diagnosing co-infections based on serology, due to the high rate of antibodies against these agents found in individuals living in endemic areas. The use of specific laboratory diagnostic procedures may provide increased awareness and recognition of tick-borne diseases.

References

1. Burgdorfer W, Barbour AG, Hayes SF, et al. Lyme disease — a tick-borne spirochetosis? Science 1982; 216:1317–1319.
2. Pancholi P, Kolbert CP, Mitchell PD, et al. Ixodes dammini as a potential vector of human granulocytic ehrlichiosis. J Infect Dis 1995; 172:1007–1012.
3. Magnarelli LA, Dumler JS, Anderson JF. Coexistence of antibodies to tick-borne pathogens of babesiosis, ehrlichiosis, and Lyme borreliosis in human sera. J Clin Microbiol 1995; 33:3054–3057.
4. Nadelman RB, Horowitz HW, Hsieh TC, et al. Simultaneous human granulocytic ehrlichiosis and Lyme borreliosis. N Engl J Med 1997; 337:27–30.
5. Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after Ixodes scapularis tick bite. N Engl J Med 2001; 345:79–84.
6. Centers for Disease Control and Prevention. Summary of notifiable diseases, United States 2000. MMWR Morb Mortal Wkly Rep 2002; 49(53):i–xxii, 1–100.
7. Schwan TG, Piesman J, Golde WT, et al. Induction of an outer surface protein on Borrelia burgdorferi during tick feeding. Proc Natl Acad Sci U S A 1995; 92:2909–2913.
8. Schwan TG, Simpson WJ. Factors influencing the antigenic reactivity of Borrelia burgdorferi, the Lyme disease spirochete. Scand J Infect Dis 1991; 77:94–101.
9. Wilske B, Preac-Mursic V, Schierz G, Busch K. Immunochemical and immunological analysis of European Borrelia burgdorferi strains. Zentralbl Bakteriol Mikrobiol Hyg [A] 1986; 263:92–102.
10. Aguero-Rosenfeld ME, Nowakowski J, McKenna DF, et al. Serodiagnosis in early Lyme disease. J Clin Microbiol 1993; 31:3090–3095.
11. Fikrig E, Telford SR 3rd, Barthold SW, et al. Elimination of Borrelia burgdorferi from vector ticks feeding on OspA-immunized mice. Proc Natl Acad Sci U S A 1992; 89:5418–5421.
12. Craft JE, Fischer DK, Shimamoto GT, Steere AC. Antigens of Borrelia burgdorferi recognized during Lyme disease. Appearance of a new immunoglobulin M response and expansion of the immunoglobulin G response late in the illness. J Clin Microbiol 1986; 78:934–939.
13. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. J Infect Dis 1993; 167:392–400.
14. Aguero-Rosenfeld ME, Nowakowski J, Bittker S, et al. Evolution of the serologic response to Borrelia burgdorferi in treated patients with culture-confirmed erythema migrans. J Clin Microbiol 1996; 34:1–9.
15. Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. J Clin Microbiol 1995; 33:419–427.
16. Liang FT, Alvarez AL, Gu Y, et al. An immunodominant conserved region within the variable domain of VlsE, the variable surface of Borrelia burgdorferi. J Immunol 1999; 163:5566–5573.
17. Van Dam AP, Kuiper H, Vos K, et al. Different genospecies of Borrelia burgdorferi are associated with distinct clinical manifestations of Lyme borreliosis. Clin Infect Dis 1993; 17:709–717.
18. Balmelli T, Piffaretti JC. Association between different clinical manifestations of Lyme disease and different species of Borrelia burgdorferi sensu lato. Res Microbiol 1995; 146:329–340.
19. Steere AC. Lyme disease. N Engl J Med 2001; 345:115–125.

20. Steere AC, Hardin JA, Malawista SE. Erythema chronicum migrans and Lyme arthritis: cryoimmunoglobulins and clinical activity of skin and joints. Science 1977; 96(4294):1121–1122.

21. Steere AC, Malawista SE, Hardin JA, et al. Erythema chronicum migrans and Lyme arthritis. The enlarging clinical spectrum. Ann Intern Med 1977; 86(6):685–898.

22. de Koning J, Bosma RB, Hoogskamp-Korstanje JAA. Demonstration of spirochetes in patients with Lyme disease with a modified silver stain. J Med Microbiol 1987; 23:261–267.

23. Berger BW, Kaplan MH, Rothenberg IR, Barbour AG. Isolation and characterization of the Lyme disease spirochete from the skin of patients with erythema chronicum migrans. J Am Acad Dermatol 1985; 13:444–449.

24. Schwartz I, Wormser GP, Schwartz JJ, et al. Diagnosis of early Lyme disease by polymerase chain reaction amplification and culture of skin biopsies from erythema migrans lesions. J Clin Microbiol 1992; 30:3082–3088.

25. Nowakowski J, Schwartz I, Liveris D, et al. Laboratory diagnostic techniques for patients with early Lyme disease associated with erythema migrans: a comparison of different techniques. Clin Infect Dis 2001; 33:2023–2027.

26. Nocton JJ, Dressler F, Rutledge BJ, et al. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis. N Engl J Med 1994; 330:229–234.

27. Barbour AG. Isolation and cultivation of Lyme disease spirochetes. Yale J Biol Med 1984; 57:521–525.

28. Berger BW, Johnson RC, Kodner C, Coleman L. Cultivation of Borrelia burgdorferi from erythema migrans lesions and perilesional skin. J Clin Microbiol 1992; 30:359–361.

29. Benach JL, Bosler EM, Hanrahan JP, et al. Spirochetes isolated from the blood of two patients with Lyme disease. N Engl J Med 1983; 308:740–742.

30. Wormser GP, Nowakowski J, Nadelman RB, et al. Improving the yield of blood cultures for patients with early Lyme disease. J Clin Microbiol 1998; 36:296–298.

31. Wormser GP, Liveris D, Nowakowski J, et al. Association of specific subtypes of Borrelia burgdorferi with hematogenous dissemination in early Lyme disease. J Infect Dis 1999; 180:720–725.

32. Schwan TG, Burgdorfer W. Antigenic changes of Borrelia burgdorferi as a result of in vitro cultivation. J Infect Dis 1987; 156:852–853.

33. Centers for Disease Control and Prevention. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep 1995; 44:590–591.

34. Aguero-Rosenfeld ME, Roberge J, Carbonaro CA, et al. Effects of OspA vaccination on Lyme disease serologic testing. J Clin Microbiol 1999; 37:3718–3721.

35. Liang FT, Steere AC, Marques AR, et al. Sensitive and specific serodiagnosis of Lyme disease by enzyme-linked immunosorbent assay with a peptide based on an immunodominant conserved region of Borrelia burgdorferi VlsE. J Clin Microbiol 1999; 37:3990–3996.

36. Gomes-Solecki MJ, Dunn JJ, Luft BJ, et al. Recombinant chimeric Borrelia proteins for diagnosis of Lyme disease. J Clin Microbiol 2000; 38:2530–2535.

37. Callister SM, Schell RF, Case KL, et al. Characterization of the borreliacidal antibody response to Borrelia burgdorferi in humans: a serodiagnostic test. J Infect Dis 1993; 167:158–164.

38. Dumler JS, Barbet AF, Bekker CPJ, et al. Reorganization of genera in the families Rickettsiaceae and Anaplasmataceae in the order Rickettsiales: unification of some species of Ehrlichia with Anaplasma, Cowdria with Ehrlichia and Ehrlichia with Neorickettsia, descriptions of six new species combinations and designation of Ehrlichia equi and 'HGE agent' as subjective synonyms of Ehrlichia phagocytophila. Int J Syst Evol Microbiol 2001; 51(Pt 6):2145–2165.

39. Anonymous. Notification that new names and new combinations have appeared in volume 51, part 6, of the IJSEM. Int J Syst Evol Microbiol 2002; 52:5–6.

40. Maeda K, Markowitz N, Hawley RC, et al. Human infection with Ehrlichia canis, a leukocytic rickettsia. N Engl J Med 1987; 316:853–856.

41. Buller RS, Arens M, Hmiel SP, et al. Ehrlichia ewingii, a newly recognized agent of human ehrlichiosis. N Engl J Med 1999; 341:148–155.

42. Misao T, Kobayashi Y. Studies on infectious mononucleosis. I. Isolation of etiologic agent from blood, bone marrow, and lymph node of a patient with infectious mononucleosis by using mice. Tokyo Iji Shinshi 1954; 71:683–686.

43. Bakken JS, Dumler JS, Chen SM, et al. Human granulocytic ehrlichiosis in the upper Midwest United States. A new species emerging? JAMA 1994; 272:212–218.

44. Bakken JS, Krueth J, Wilson-Nordskog C, et al. Clinical and laboratory characteristics of human granulocytic ehrlichiosis. JAMA 1996; 275:199–205.

45. Aguero-Rosenfeld ME, Horowitz HW, Wormser GP, et al. Human granulocytic ehrlichiosis (HGE): a case series from a single medical center in New York State. Ann Intern Med 1996; 125:904–908.

46. Horowitz HW, Kilchevsky E, Haber S, et al. Perinatal transmission of the agent of human granulocytic ehrlichiosis. N Engl J Med 1998; 339:375–378.

47. Bakken JS, Aguero-Rosenfeld ME, Tilden RL, et al. Serial measurements of hematologic counts during the active phase of human granulocytic ehrlichiosis. Clin Infect Dis 2001; 32:862–870.

48. Goodman JL, Nelson C, Vitale B, et al. Direct cultivation of the causative agent of human granulocytic ehrlichiosis. N Engl J Med 1996; 334:209–215.

49. Kalantarpour F, Chowdhury I, Wormser GP, Aguero-Rosenfeld ME. Survival of the human granulocytic (HGE) agent under refrigeration conditions. J Clin Microbiol 2000; 38:2398–2399.

50. Walls JJ, Caturegli P, Bakken JS, et al. Improved sensitivity of PCR for diagnosis of human granulocytic ehrlichiosis using epank1 genes of Ehrlichia phagocytophila-group ehrlichiae. J Clin Microbiol 2000; 38:354–356.

51. Sumner JW, Nicholson WL, Massung RF. PCR amplification and comparison of nucleotide sequences from the groESL heat shock operon of Ehrlichia species. J Clin Microbiol 1997; 35:2087–2092.

52. IJdo JW, Meek JI, Cartter ML, et al. The emergence of another tickborne infection in the 12-town area around Lyme, Connecticut: human granulocytic ehrlichiosis. J Infect Dis 2000; 181:1388–1393.

53. Dumler JS, Asanovich KM, Bakken JS, et al. Serologic cross-reactions among Ehrlichia equi, Ehrlichia phagocytophila, and human granulocytic Ehrlichia. J Clin Microbiol 1995; 33:1098–1103.

54. Aguero-Rosenfeld ME, Kalantarpour F, Baluch M, et al. Serology of culture-confirmed cases of human granulocytic ehrlichiosis. J Clin Microbiol 2000; 38:635–638.

55. IJdo JW, Zhang Y, Hodzic E, et al. The early humoral response in human granulocytic ehrlichiosis. J Infect Dis 1997; 176:687–692.

56. Ravyn MD, Goodman JL, Kodner CB, et al. Immunodiagnosis of human granulocytic ehrlichiosis by using culture-derived human isolates. J Clin Microbiol 1998; 36:1480–1488.
57. Bakken JS, Goellner P, Van Etten M, et al. Seroprevalence of human granulocytic ehrlichiosis among permanent residents of northwestern Wisconsin. Clin Infect Dis 1998; 27:1491–1496.
58. Aguero-Rosenfeld ME, Donnarumma L, Zentmaier L, et al. Seroprevalence of antibodies that react with Anaplasma phagocytophila, the agent of human granulocytic ehrlichiosis, in different populations in Westchester County, New York. J Clin Microbiol 2002; 40:2612–2615.
59. Zhi N, Ohashi N, Rikihisa Y, et al. Cloning and expression of the 44-kilodalton major outer membrane protein gene of the human granulocytic ehrlichiosis agent and application of the recombinant protein to serodiagnosis. J Clin Microbiol 1998; 36:1666–1673.
60. Murphy CI, Storey JR, Recchia J, et al. Major antigenic proteins of the agent of human granulocytic ehrlichiosis are encoded by members of a multigene family. Infect Immun 1998; 66:3711–3718.
61. Homer MJ, Aguilar-Delfin I, Telford SR 3rd, et al. Babesiosis. Clin Microbiol Rev 2000; 13:451–469.
62. Herwaldt BL, Kjentrup AM, Conrad PA, et al. Transfusion-transmitted babesiosis in Washington State: first reported case caused by a WA1-type parasite. J Infect Dis 1997; 175:1259–1262.
63. Krause PJ, Spielman A, Telford SR 3rd, et al. Persistent parasitemia after acute babesiosis. N Eng J Med 1998; 339:160–165.
64. Krause PJ, Telford SR 3rd, Spielman A, et al. Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. JAMA 1996; 275:1657–1660.
65. Krause PJ, Telford S 3rd, Spielman A, et al. Comparison of PCR with blood smear and inoculation of small animals for diagnosis of Babesia microti parasitemia. J Clin Microbiol 1996; 34:2791–2794.
66. Persing DH, Herwaldt BL, Glaser C, et al. Infection with a babesia-like organism in northern California N Engl J Med 1995; 332:298–303.

Lyme Disease Trends — Dutchess County, New York, 1992–2000

CATHERINE C. CHOW, M.D., M.P.H.[1], ANDREW S. EVANS, JR.[2], CANDACE M. NOONAN-TOLY[3], DENNIS WHITE, PH.D.[4],
GERALDINE S. JOHNSON[5], SPENCER J. MARKS, M.P.A.[6], MICHAEL C. CALDWELL, M.D., M.P.H.[7],
AND EDWARD B. HAYES, M.D.[8]

Abstract

Background: Lyme disease is a vector-borne infectious disease, accounting for more than 95% of all reported vector-borne illness in the United States. From 1992–2000, Dutchess County reported more cases of Lyme disease than any other county in the United States, consistently ranking among the top ten in incidence rates. We analyzed 1992–2000 Dutchess County Lyme disease surveillance data to characterize Lyme disease trends, identify high-risk populations, and examine the frequency of the characteristic lesion, erythema migrans.

Methods: A Lyme disease case was defined as a person with physician-diagnosed erythema migrans or at least one "late" manifestation of the disease, with laboratory confirmation. A surveillance database of cases reported in Dutchess County from 1992–2000 was obtained from the New York State Department of Health. Annual incidence rates by age, gender, race, ethnicity, and ZIP codes, and frequency of erythema migrans were calculated.

Results: From 1992 through 2000, a total of 9,548 cases of Lyme disease were reported by Dutchess County to the New York State Department of Health, for a crude mean annual incidence rate of 400 cases per 100,000 persons per year. The incidence rate peaked at 683/100,000 in 1996, and then declined from 1998 to 2000. A bimodal age distribution was seen, with the initial peak among children aged 5–9 years (617/100,000) and the second peak among adults aged 60–64 years (627/100,000). A male preponderance was clearly seen between the ages of 5–19 years, and beyond the age of 60 years. Highest incidence rates were reported in central Dutchess County. Onset of illness occurred most frequently in June, July, and August. Ninety-four percent of cases occurred among the predominantly white population, which had the highest incidence rate (431/100,000) among the races. Incidence rate for non-Hispanics was more than double that for Hispanics. Eighty-one percent of reported cases had erythema migrans.

Conclusions: While some prevention programs could be broadly targeted to the entire Dutchess County population, other interventions might be most effective if they focused on the high-risk population groups and areas defined in this report. The high proportion of cases with erythema migrans suggests that early diagnosis and treatment should be effective in reducing late-stage complications of Lyme disease in Dutchess County. Surveillance data for other endemic counties and states can be similarly analyzed to enhance and monitor local prevention programs.

Key Words: Lyme disease, *Borrelia burgdorferi*, incidence, surveillance.

Introduction

LYME DISEASE IS A VECTOR-BORNE infectious disease, accounting for more than 95% of all reported vector-borne illness in the United States in 1996 (1). First recognized in North America in 1975, Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which is transmitted to humans by ticks of the species *Ixodes* (deer ticks). Measures that may be effective in preventing Lyme disease include wearing protective clothing, using insect repellents, and the early detection and removal of ticks. Antibiotic prophylaxis given within 72 hours of a deer tick bite may be effective in highly endemic areas (2). Exclusion or removal of deer, removal of leaf litter, and acaracide application to rodent, deer, and tick habitats may be useful in reducing tick populations.

---

[1]Epidemic Intelligence Service, Division of Vector-Borne Infectious Diseases, and [8]Division of Vector-Borne Infectious Diseases, and Chief, Epidemiology Section, Bacterial Zoonoses Branch, Centers for Disease Control and Prevention, Fort Collins, CO; [2]Senior Public Health Advisor, [6]Director, Division of Communicable Diseases, and [7]Commissioner of Health, Dutchess County Department of Health, Poughkeepsie, NY; and [3]Statistical Unit, [4]Director, Arthropod-Borne Disease Program, and [5]Research Scientist, New York State Department of Health, Albany, NY.

The study was done at the Epidemic Intelligence Service and the Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, CO. It is based on data received from the Dutchess County Department of Health, Poughkeepsie, NY and the New York State Department of Health, Albany, NY.

Address all correspondence to Dr. Catherine C. Chow, Centers for Disease Control and Prevention, P.O. Box 2087, Fort Collins, CO 80522.

Accepted for publication December 24, 2002.
Grant support: none
Conferences: none

The Centers for Disease Control and Prevention (CDC) initiated Lyme disease surveillance in the United States in 1982. Surveillance in Dutchess County soon followed, in 1986, when reporting of Lyme disease was mandated in New York State. In 1991, Lyme disease was added to the list of nationally notifiable diseases. From 1992 to 2000, the annual reported incidence of Lyme disease in the United States nearly doubled to 17,730 cases (3). During this time period, Dutchess County reported more cases of Lyme disease than any other county in the U.S., consistently ranking among the top ten counties in incidence rates. In 2001, the American Lyme Disease Foundation and the Dutchess County Department of Health (DCDOH), with funding through a cooperative agreement with the CDC, initiated a community-based Lyme disease prevention program in Dutchess County.

We analyzed Dutchess County Lyme disease surveillance data for 1992–2000, to assess the public health status of Lyme disease in Dutchess County. We characterized Lyme disease trends, identified high-risk populations, and examined the frequency of the characteristic lesion, erythema migrans (EM), among the reported cases.

Materials and Methods

For surveillance purposes, a case of Lyme disease was defined as a person with physician-diagnosed EM or at least one "late" manifestation of the disease (rheumatic, neurologic, cardiac, or ophthalmic), with laboratory confirmation.

The DCDOH receives reports of Lyme disease from health care providers and laboratories. Laboratories report positive results via either a weekly facsimile or the recently initiated Electronic Clinical Laboratory Reporting System (ECLRS). Clinical and laboratory information necessary to make case determinations is gathered, and confirmed cases are entered onto DCDOH forms. These data are transferred to the New York State Department of Health (NYSDOH) via the electronic Health Information Network, where the submitted cases are again evaluated and confirmed by NYSDOH staff. Surveillance data from NYSDOH are then forwarded to the CDC National Electronic Telecommunication Surveillance System (NETSS).

Lyme disease surveillance data for 1992–2000 was obtained from the NYSDOH Statistical Unit. Information about each case included: (a) demographics, such as age, sex, and ZIP code of residence; (b) timing of illness, such as date of symptom onset, date of diagnosis, and date of reporting; and (c) for recent years, presence or absence of EM. Descriptive analysis was performed using Microsoft EXCEL and EpiInfo 2000 computer programs (4). Incidence rates by age group and sex were calculated using annual Dutchess County population estimates from the U.S. census. Incidence rates by race and ethnicity were calculated using 1996 Dutchess County population estimates from the U.S. census. Incidence rates by ZIP code were calculated using year 2000 population estimates within the ZIP code boundaries provided by CACI International in ArcMap, and then mapped using categories determined by Jenks optimization (5).

Results

Temporal Trends

From 1992 through 2000, a total of 9,548 cases of Lyme disease were reported by Dutchess County to the NYSDOH, for a mean annual incidence rate of 400 reported cases per 100,000 persons per year. Over the nine-year period, the annual incidence per 100,000 persons peaked at 683 in 1996, dropped to 389 the following year, then decreased from 579 in 1998 to 385 in 2000 (Fig. 1). Dutchess County reported 25% of the total Lyme disease cases recorded by New York State during 1992–2000. The Dutchess County trend is somewhat different from that of New York State (excluding Dutchess County data) (Fig. 2), as well as that of the United States (Fig. 3).

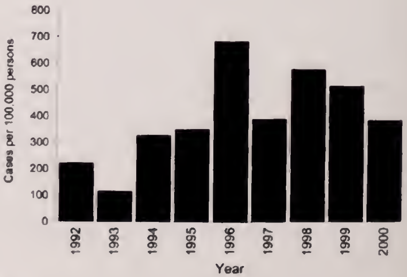

Fig. 1. Incidence rate of reported cases of Lyme disease — Dutchess County, New York, 1992–2000.

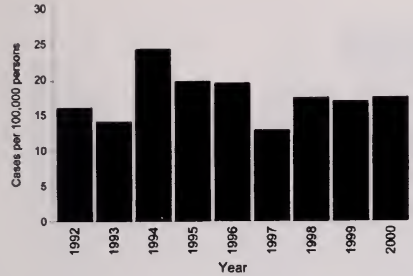

Fig. 2. Incidence rates of reported cases of Lyme disease — New York State with exclusion of Dutchess County, 1992–2000.

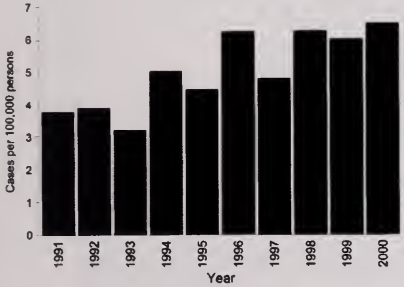

Fig. 3. Incidence rates of reported cases of Lyme disease — United States, 1991–2000.

Seasonality

Information regarding date of symptom onset was available for 9,453 reported cases (99.0%). When numbers of reported cases were plotted by reported month of symptom onset, the peak month of symptom onset was shown to be July (3,047 cases), followed by June (2,391 cases) and August (1,249 cases), respectively (Fig. 4).

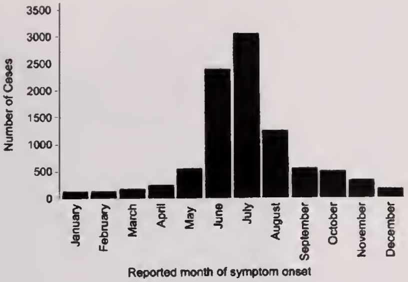

Fig. 4. Month of Lyme disease onset for reported cases — Dutchess County, New York, 1992–2000.

Spatial Distribution

Information regarding the ZIP code of residence was available for 9,539 reported cases (99.9%). Of these records, 9,318 indicated ZIP codes that are currently being used in Dutchess County (97.7% of ZIP codes). The three ZIP code areas reporting the highest numbers of cases were within Poughkeepsie, Hopewell Junction, and Wappinger Falls, all in the southwestern region of Dutchess County. However, these three areas were also within the four most populous ZIP codes. The three ZIP code areas reporting the highest incidence rates of Lyme disease were in Millbrook, Verbank, and Salt Point, located in central Dutchess County (Fig. 5).

Demographics

Data regarding both gender and age were reported for 9,477 cases (99.3%). The distribution of mean annual incidence rates by age was bimodal. The initial peak occurred among children between the ages of 5–9 years. The second peak occurred among adults between the ages of 60–64 years, one decade older than the peak reflected in the 1992–1998 United States data (6). Lyme disease incidence rates for persons aged 40–59 years were slightly higher in females; however, a male preponderance was clearly seen between the ages of 5–19 years, and beyond 60 years (Fig. 6).

Race and Ethnicity

Data regarding race was reported for 9,202 cases (96.4%). The majority of reported Lyme disease cases (93.6 %), and the highest incidence rate, occurred among whites, with a mean annual incidence rate of 431 per 100,000 persons. The incidence rates among the county's minority populations were much lower (Fig. 7).

Data regarding ethnicity was reported for 8,732 (91.5%) cases. Among these cases, the mean annual incidence rate per 100,000 persons for non-Hispanic residents (379) was more than double that for Hispanic residents (157).

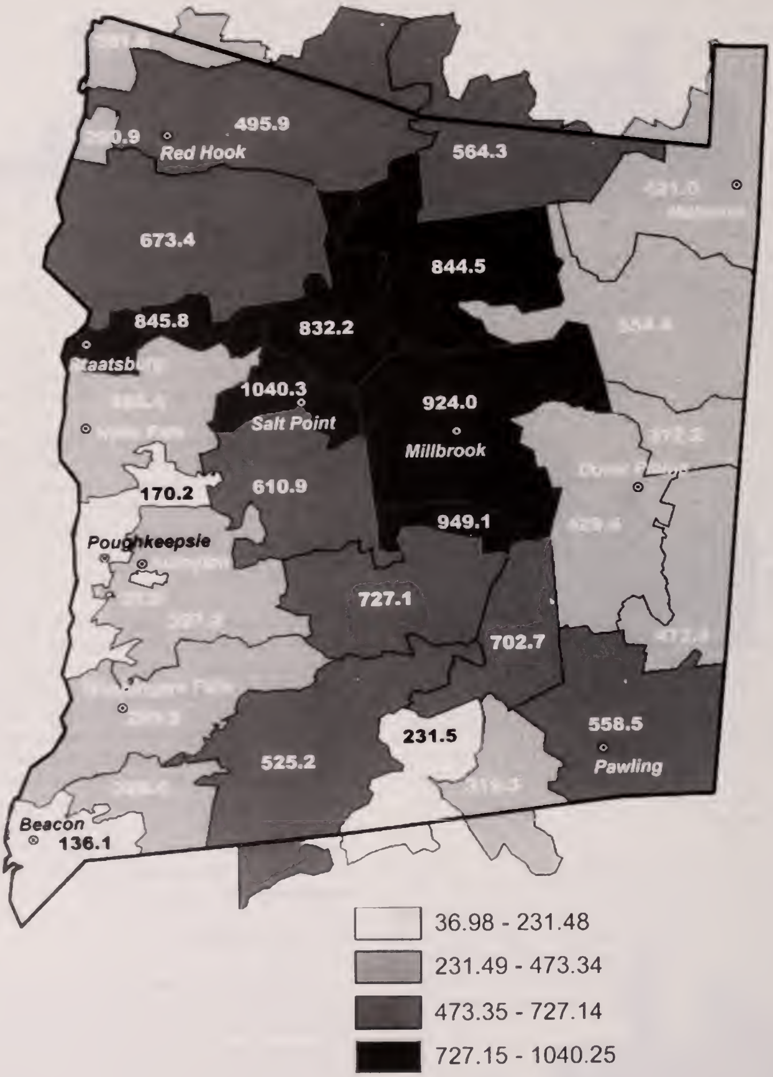
495.9
Red Hook
564.3
673.4
844.5
845.8
832.2
Staatsburg
1040.3
Salt Point
924.0
Millbrook
170.2
610.9
949.1
Poughkeepsie
727.1
702.7
558.5
Pawling
231.5
525.2
Beacon
136.1
36.98 - 231.48
231.49 - 473.34
473.35 - 727.14
727.15 - 1040.25

Fig. 5. Incidence rates of reported Lyme disease cases by ZIP codes — Dutchess County, New York, 1992 – 2000. The three ZIP code areas reporting the highest numbers of cases were within Poughkeepsie, Hopewell Junction, and Wappinger Falls, in the southwestern region of Dutchess county. Hopewell Junction, not shown above, is approximately 7 miles east of Wappinger Falls. The three ZIP code areas reporting the highest incidence rates of Lyme disease were in Millbrook, Verbank, and Salt Point, located in central Dutchess County. Verbank, not shown above, is approximately 4 miles south of Millbrook.

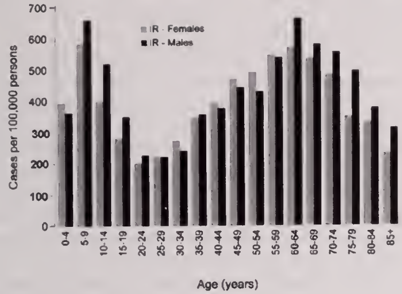

Fig. 6. Mean annual incidence rate (IR) of Lyme disease cases by age group and sex — Dutchess County, New York, 1992–2000.

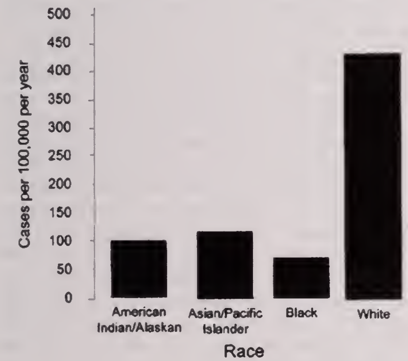

Fig. 7. Mean annual incidence rates of reported Lyme disease cases by race — Dutchess County, New York, 1992–2000.

Frequency of Erythema Migrans

Computerized data regarding the presence or absence of EM were available after 1997. Of the 5,021 Lyme disease reports entered between 1997 and 2000, 4,962 (98.8%) contained data regarding EM. EM was reportedly present in 4,039 (81.2%) of these cases. A higher percentage of EM was noted among reported Lyme disease cases in 2000 (90.4%) than in the preceding years (77.1% in 1999, 80.4% in 1998, 79.8% in 1997). More than 50% of cases with month of onset from May through December had EM, and more than 90% of those with month of onset in June and July had EM. Among cases reporting the month of onset as December through March, the percentage of EM ranged from 23.4–30.5%.

Data regarding both date of symptom onset and date of diagnosis were available for 9,399 (98.4%) reported cases. Of these, 5 cases had obvious errors, reporting dates of diagnosis that preceded dates of symptom onset. Among the remaining cases, the median interval between onset of symptoms and diagnosis was 3 days, with a range of 0 to 8,783 days. The reported delay in diagnosis from the date of symptom onset was greater than five years in 5 (0.05%) of these cases; the case with the longest duration of delay reported symptom onset in 1972 and diagnosis of Lyme disease in 1996. Data regarding symptom onset, date of diagnosis, and EM were available for 4,957 (98.7%) of the 5,021 Lyme disease reports from 1997 to 2000. The median interval between onset of symptoms and diagnosis was 2 days (range 0–1,382 days) for cases with EM, versus 5 days (range 0–1,616 days) for cases without EM. The proportion of cases with EM decreased as the interval from symptom onset to diagnosis increased (Fig. 8).

Discussion

Whereas the annual incidence rate for Lyme disease in Dutchess County peaked in 1996 and then declined from 1998 to 2000 (prior to the initiation of the community prevention program), the incidence rate for the remainder of New York State stayed relatively stable through 2000, and the incidence rate in the United States increased slightly in 2000. These differ-

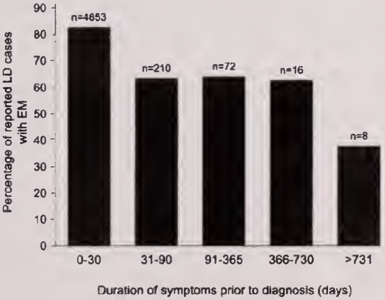

Fig. 8. Presence of erythema migrans by duration of symptoms prior to diagnosis.

ences may reflect real differences in Lyme disease incidence, but could also be largely or partially due to changes in local and state surveillance practices. There were personnel changes and minor modifications of surveillance practices at both state and local levels during this time. Awareness and reporting of Lyme disease in Dutchess County might have increased in 1996 as the result of a Lyme disease vaccine trial (7). The outbreak of West Nile virus in New York was first recognized in late August of 1999 (8). The emergence of this new public health threat shifted limited local personnel resources away from Lyme disease surveillance, and may have decreased or delayed the reporting of 1999 and 2000 Lyme disease cases.

The highest Lyme disease incidence rates in Dutchess County were reported in the central region, whereas the lowest incidence rates were reported in the southwestern area. The reason for this distribution of incidence is not clear. The incidence of Lyme disease at the state and regional levels in Connecticut has been shown to parallel the abundance of *Ixodes scapularis* nymphs and *Borrelia burgdorferi*-infected nymphs (9). Local variations in tick densities and tick infection rates may play a role in the distribution of Lyme disease in Dutchess County, but detailed data on entomologic indices to assess such effects are not currently available. The factors that influence the annual abundance of *Ixodes scapularis* are not well understood (9), but environmental variables postulated to affect tick habitat suitability include presence of forested areas, proximity to watersheds, soil types, and residential setting (10). Spatial analyses of Lyme disease incidence rates in New York State have indicated that Lyme disease has spread northward and westward in an advancing wave from a high-incidence area in Westchester County, most likely due to movement of vector hosts (11). Local human behaviors that affect the level of exposure to ticks may also play a part in the geographic distribution of Lyme disease. Finally, as discussed above, local variations in case reporting and other surveillance biases may influence the observed distribution of the disease.

The highest reported incidence rate of Lyme disease in Dutchess County occurred among the white, non-Hispanic population. The reason for the disparate rates among different age groups, genders, races and ethnicities is not clear, but may be explained by differential tick exposure, differential access to health care, diagnostic bias or reporting bias. The large number of cases reported with unknown ethnicity limits the certainty about differences in ethnic-specific incidence rates.

The seasonal trend for reported Lyme disease cases from Dutchess County was consistent with results extracted from the national Lyme disease surveillance data collected from 1992–1998, as well as results from other epidemiologic studies (6). The months of June, July, and August pose the highest risk for Lyme disease, since this is when both seasonal feeding activity of nymphal *Ixodes scapularis* and human outdoor activity are highest (12).

While some prevention programs could be broadly targeted to the entire Dutchess County population, other interventions might be most effective if special emphasis were given to the high-risk population groups and areas defined in this report. Educational strategies advocating personal protective measures might be most effective if focused on young children and older adults, especially the older male population. Such strategies should be timed to precede the peak transmission season in late spring and early summer. Ecological interventions to reduce tick densities might have the greatest impact if targeted to the central areas, where incidence is highest and to the southwest areas, where the greatest numbers of cases occur.

In a study of the residents of Great Island, Massachusetts, conducted from 1979–1983, EM was found to occur in 61–86% of those with the disease (13). More recent studies suggest that nearly 90% of people with Lyme disease develop EM (14–16). In Dutchess County, EM was diagnosed in 80–90% of reported Lyme disease cases.

Most cases of Lyme disease are acquired during the summer months, and this is reflected in the high proportion of cases that are reported with EM during the summer (17). The diagnosis of Lyme disease cases that do not have EM may be delayed until fall or winter months, even though the infection was acquired during the summer. However, the proportion of Lyme disease cases reporting EM in Dutchess County remained above 50% well into November and above 20% between December and March. While EM may be misdiagnosed in some of these cases (17), this finding supports previous studies indicating that adult ticks, which may be active in colder months, play a minor yet noticeable role in the transmission of Lyme disease to humans (18–20). Educational interventions to prevent Lyme disease may need to stress the potential for year-round transmission of Lyme disease.

Other than the outliers in whom diagnosis was extensively delayed, most Lyme disease cases were diagnosed in a timely manner. The high proportion of cases reported with EM in Dutchess County indicates that most cases of Lyme disease in that area are diagnosed in the early stages. Not surprisingly, patients without EM tended to be diagnosed later than those with EM, as recognition of early-stage Lyme disease in the absence of EM can be difficult. The timely diagnosis and treatment of patients with early Lyme disease is an important tertiary prevention strategy that can prevent late-stage complications of Lyme disease. This fact should be emphasized in prevention messages to health care providers and the general public.

Conclusion

Dutchess County, where Lyme disease is most prevalent, experienced an increase in incidence rate in the early 1990s. Despite a decline in the incidence rate between 1998 and 2000, the high number of cases that continue to be reported in Dutchess County remains a concern. Analysis of Dutchess County Lyme disease surveillance data revealed that the highest incidence rates were reported in the summer, among white, non-Hispanic males in early childhood and late adulthood, with a focal distribution in central Dutchess County. While some prevention programs could be broadly targeted to the entire Dutchess County population, other interventions might be most effective if special emphasis were given to the high-risk population groups and areas defined in this report. The high proportion of cases with EM suggests that tertiary prevention through early diagnosis and treatment should be effective in reducing late-stage complications of Lyme disease in Dutchess County. Surveillance data for other counties where Lyme disease is endemic can be analyzed similarly to enhance and monitor local prevention programs.

References

1. Rahn DW, Evans J. Lyme disease. Philadelphia (PA): American College of Physicians; 1998. p. 7.
2. Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. N Engl J Med 2001; 345:79–84.
3. Lyme disease — United States, 2000. MMWR Morb Mortal Wkly Rep 2002; 51(02):29–31.
4. Dean AG, Arner TG, Sangam S, et al. EpiInfo, Version 1.1.2: a database and statistics program for public health professionals for use on Windows® 95, 98, NT, and 2000 computers. Atlanta: Centers for Disease Control and Prevention; 2000.
5. Shaner J, Wrightsell J. ArcMap 2000 in ArcGIS 8. ESRI, Redlands (CA), 1999–2001.
6. Surveillance for Lyme disease — United States, 1992–1998. MMWR Morb Mortal Wkly Rep 2000; 49(SS-3):1–11.
7. Lyme disease — United States, 1996. MMWR Morb Mortal Wkly Rep 1997; 46:531–535.
8. Outbreak of West Nile-like viral encephalitis — New York, 1999. MMWR Morb Mortal Wkly Rep 1999; 48(38):845–849.
9. Stafford, KC 3rd, Cartter, ML, Magnarelli LA, et al. Temporal correlations between tick abundance and prevalence of ticks infected with Borrelia burgdorferi and increasing incidence of Lyme disease. J Clin Microbiol 1998; 36(5):1240–1244.
10. Cromley EK, Cartter ML, Mrozinski RD, Ertel SH. Residential setting as a risk factor for Lyme disease in a hyperendemic region. Am J Epidemiol 1998; 147:472–477.
11. Glavanakov S, White DJ, Caraco T, et al. Lyme disease in New York State: spatial pattern at a regional scale. Am J Trop Med Hygiene 2001; 65:538–545.
12. Ostfeld RS. The ecology of Lyme-disease risk. American Scientist 1997; 85:338–346.
13. Steere AC, Taylor E, Wilson ML, et al. Longitudinal assessment of the clinical and epidemiological features of Lyme disease in a defined population. J Infect Dis 1986; 154:295–300.
14. Gerber MA, Shapiro ED, Burke GS, et al. Lyme disease in children in southeastern Connecticut. N Engl J Med 1996; 335:1270–1274.
15. Wormser GP, McKenna D, Nadelman RB, et al. Lyme disease in children [letter]. N Engl J Med 1997; 336:1107.
16. Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme disease with recombinant Borrelia burgdorferi outer-surface lipoprotein A with adjuvant. Lyme Disease Vaccine Study Group. N Engl J Med 1998; 339(4):209–215.
17. Falco RC, McKenna DF, Daniels TJ, et al. Temporal relation between Ixodes scapularis abundance and risk for Lyme disease associated with erythema migrans. Am J Epidemiol 1999; 149(8):771–776.
18. Schulze TL, Bowen GS, Lakat MF, et al. The role of adult Ixodes dammini (Acari: Ixodidae) in the transmission of Lyme disease in New Jersey, USA. J Med Entomol 1985; 22(1):88–93.
19. Couch P, Johnson CE. Prevention of Lyme disease. Am J Hosp Pharm 1992; 49(5):1164–1173.
20. Steere AC. Lyme disease. N Engl J Med 1989; 321(9):586–596.

INFORMATION FOR AUTHORS

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of The Mount Sinai Hospital*, is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and other major databases. The abstract and full text of each published article is posted on *The Journal's* web site <www.mssm.edu/msjournal> where it can be accessed by the reader. *The Journal*'s web site is linked to that of the National Library of Medicine. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcomed. *The Journal* generally follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as revised in 1997 and modified by *The Journal* to conform to the style employed by it. *The Journal* aims at responding to authors of manuscripts within 8 weeks of submission.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@mssm.edu; world wide web: www.mssm.edu/msjournal.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and either (3) the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in *The Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal*'s office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations and a disk (see below). **Manuscripts must be computer generated, double spaced throughout (including references, legends, and tables)**, on one side of $8^{1}/_{2}$ (11 inch white bond paper with **one inch** margins. The title page must be entirely separate and should designate the location(s) where the work was done, and the name and address of the corresponding author. The abstract page(s) should be numbered sequentially as i, ii, iii, etc. A separate page should be used for each table. The legends, in numerical sequence, should be typed together on one or more pages (if needed). A separate page, or pages, should list the references in the sequential order they are cited for the first time in the narrative text. A disk should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted (Windows, MAC), and the software used (WordPerfect, MS Word, etc.). PC format is preferred, but a high-density, formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or WordPerfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page(s) or in legends. Define all abbreviations on first use in the body of the manuscript. All abbreviations used in a table must be defined at the bottom of the table.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher, giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office (or its equivalent) which supervises such work.

Title Page. This page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, and middle initial(s), if any, and not more than two academic degrees; (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and telephone and FAX numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom an offprint is to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and (9) **a running head of fewer than 40 letter spaces.** At the bottom of the title page, **list 3 to 10 key words or phrases** to facilitate computer searches in accord with medical subject headings from *Index Medicus*. If more than one sheet is needed, label the supplemental sheet as "Title Page (cont.)."

Abstract. All articles must include an abstract of not more than 400 words. The pages containing the abstract should be numbered sequentially as i, ii, iii, etc. This abstract will be published in *The Journal* with the article. Enough detail should be provided in the abstract so that it will be sufficiently informative to stand alone when placed on *The Journal*'s web page (prior to publication of the entire article in *The Journal*). Abstracts should be double spaced. Abstracts for manuscripts specifically describing original clinical and/or laboratory research should be structured in four paragraphs:

Background: what problem(s) was (were) addressed;
Methods: how the study was performed;
Results: the most significant results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page and also after the abstract to facilitate computer searches. **Repeat at the end of the abstract the same key words which are listed on the title page.**

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning, in conformity with the style used by *The Journal*. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high-contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of $3^{1}/_{8}$ inches. **The type of stain and power of magnification (e.g., 10X, 40X, 100X, etc.) must be indicated in the relevant legend**. Electron photomicrographs should have internal scale markers. On the back of each print and photograph, affix a gum label on which the number of the figure has been written to correspond to its identification in the text, as well as the title of the manuscript, first author's last name, and the word "top" and an arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial features should be masked to prevent identification of the subject unless they include details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

The Journal does not publish color images unless the author is willing to pay for the additional expense involved. Should the author wish to consider publishing images in color, 3 copies of each color print must be included with the manuscript. If the manuscript is accepted, the author will be informed of the extra cost involved. A check for this amount must be received prior to publication. If, however, the author wishes to have color images appear **only in *The Journal's* web page version** of the article, one copy of each color print (rather than 3) along with the 3 black and white glossy prints must be submitted with the manuscript. The web page version of the manuscript will not involve additional expense to the author.

Illustrations may be submitted in electronic form, in format compatible with Adobe Photoshop (6.0 or lower) or Adobe Illustrator (8.0 or lower), or in .jpeg or .tif. Color illustrations must be in CYMK.

Legends. Legends should not duplicate the text. They should appear together in numerical order, typed double spaced, on one or more pages following the text. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle," etc.) or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Footnotes. Except as noted above in the section "Units of Measurement," the use of footnotes is to be avoided. All relevant information should be incorporated directly into the narrative text, and appropriately cited as noted below in the section "References."

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (**TABLE 1**, etc., in bold type) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text, and type the title, *in italics*, on a separate line below the table's number. Identify all abbreviations and/or symbols used in the table in a footnote at the bottom of the table.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., **Cytomegalovirus (1), steroids (2, 3), and recreational drugs (4-6) have all been implicated (7).** Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus*. The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled "References" are illustrated in the version of "Uniform Requirements" published in *The New England Journal of Medicine* referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style shown in the examples below. The list of references should not be formatted as "Endnotes."

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.
2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309–315.
3. Couser WG. Glomerular diseases. In: Stein J, editor. Internal medicine. 2nd ed. Boston: Little Brown; 1987. pp. 834—861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then "et al."

A citation to an article that has not been published in print (journal, book) and that has been obtained by accessing a website must include, in addition to the names of the authors and the title of the article, the precise uniform resource locator (URL) address at which the article can be found and accessed. This address can usually be found as a long stream of characters and numbers after the prefix "http://www.........."

References to unpublished data (unless the information is in press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission.

If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.

Proofs. A revised, copy-edited manuscript will be sent to the corresponding author as soon as it is available, for necessary corrections only. **Stylistic changes should not be made**. All corrections should be made on this copy, which must be returned to the *Journal* office as soon as possible (see "Communications" above). This corrected, revised, edited version of the manuscript will be sent to the printer for typesetting directly from a disk. "Galleys" will not be sent to the corresponding author for review.

Offprint Orders. A "Request for Offprints" form will be sent to the corresponding author. If offprints are desired, the form must be returned to the editorial office. When the article is scheduled for publication, an "Offprint Order Form" and "Shipping Label" will be sent to the corresponding author. These must be completed and returned with a check for the exact amount in US dollars made out to *The Mount Sinai Journal of Medicine*. Please indicate on the check the last name of the first author, and the title of the article. If, for one reason or another, an "Offprint Order Form" and "Shipping Label" are not received by the corresponding author, they may be obtained directly from the *Journal* office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the total number of printed pages and whether covers are desired. The cost of delivery must be added to the cost of the offprints. Information on cost of other than routine delivery can be obtained from the *Journal* office.

05/2003

THE
MOUNT SINAI JOURNAL
OF MEDICINE

LEVY LIBRARY, MT. SINAI SCHOOL OF MEDICINE
3 4805 0728745 7

Forthcoming: Grand Rounds

Glycoxidation: The Menace of Diabetes and Aging
Helen Vlassara and
Marcia Rashelle Palace
Mount Sinai School of Medicine

Primary Biliary Cirrhosis: A Mount Sinai Perspective
Nancy Bach and Joseph A. Odin
Mount Sinai School of Medicine

Congestive Heart Failure: Guidelines for the Primary Care Physician
Ira Galin and David A. Baran
Mount Sinai School of Medicine

Gender Differences in Pulmonary Disease
Cynthia F. Caracta
Mount Sinai School of Medicine

Cardiovascular Disease in Women
W. Lane Duvall
Mount Sinai School of Medicine

Theme Issues

Ethics 2001 — Medicine, Money and Morals
Rosamond Rhodes and Daniel A. Moros, Editors

Minimally Invasive Vascular Surgery: The Evolution of Endovascular Therapy
Michael L. Marin, Larry Hollier, and Valentin Fuster, Editors

Available now:

Methadone Symposium – Part 1:2000
Volume 67: Numbers 5 & 6. 125 pages, $40.00
Methadone Symposium – Part 2:2001
Volume 68: Number 1. 78 pages, $25.00

Gastroenterology and Hepatology
at The Mount Sinai Hospital 1852–2000
Volume 67: Number 1. Part 1:2000 94 pages $20.0
Volume 67: Number 3. Part 2:2000 89 pages $20.0
Volume 68: Number 2. Part 3:2001 80 pages $25.0

Visit our web page — http://www.mssm.edu/msjournal

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 70 NUMBER 4 SEPTEMBER 2003

CONTENTS

GRAND ROUNDS

Gender Differences in Pulmonary Disease *Cynthia F. Caracta* 215

Evolving Rationale for Angiotensin-Converting Enzyme Inhibition in Chronic Heart Failure *Anita Banerjee, Ashok Talreja, Edmund H. Sonnenblick, and Thierry H. LeJemtel* 225

Glycoxidation: The Menace of Diabetes and Aging *Helen Vlassara and Marcia Rashelle Palace* 232

Primary Biliary Cirrhosis: A Mount Sinai Perspective *Nancy Bach and Joseph A. Odin* 242

GENERAL ARTICLES

Congestive Heart Failure: Guidelines for the Primary Care Physician *Ira Galin and David A. Baran* 251

A Rare Cause of Pituitary Stalk Enlargement and Panhypopituitarism *Shehzad Basaria, Julie S. Krop, and Milena Braga-Basaria* 265

CLASSICS IN MEDICINE

Editors' Note: Imaging in Medicine 268

Intravenous Urography by Means of the Sodium Salt of 5-Iodo-2-Pyridon-N-Acetic Acid *Moses Swick* 269

Intravenous Urography (Swick Method) *Leopold Jaches* 280

Announcement of 2002 Awards 288

Information for Authors i

Required Form C3

SAINT BARNABAS HEALTH CARE SYSTEM

LIBERTY HEALTHCARE SYSTEM, INC.

Veterans Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by the Mount Sinai Medical Center of New York and has the following affiliates: Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY; Saint Barnabas Health Care System, Livingston, NJ; Newark Beth Israel Medical Center, Newark, NJ; Liberty HealthCare System, Inc., Jersey City, NJ.

Editor-in-Chief

Sherman Kupfer, M.D.

Associate Editors

Harriet S. Gilbert, M.D.
Leslie A. Kuhn, M.D.
Philip S. Ledereich, M.D.

Administrative Assistant

Ron Stein

Assistant Editor for Housestaff

Leora Horwitz, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

Scott H. Barnett, M.D.
J. Hugh Baron, D.M.
David H. Bechhofer, Ph.D.
Constantin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Donald Brief, M.D.
Daniel Buchbinder, D.M.D, M.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., M.P.H., M.P.P.
William H. Constad, M.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Jack Hirschowitz, M.B., Ch.B.
Fred M. Jacobs, M.D., J.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M. Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkovitz, M.D.
Dana M. Lewis, M.L.S.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Myron Miller, M.D.
Richard Panush, M.D.
Barbara E. C. Paris, M.D.
Jerome G. Porush, M.D.
Georges R. Ramalanjaona, M.D., D.Sc.
Veronica A. Ravnikar, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Tibor Rohacs, M.D.
Gregory J. Rokosz, D.O., J.D.
Joshua Rosenblatt, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Harry Schanzer, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Janet B. Serle, M.D.
Phyllis Shaw, Ph.D.
Scott H. Sicherer, M.D.
Barry D. Stimmel, M.D.
Nelson N. Stone, M.D.
Max Sung, M.D.
Jules A. Titelbaum, M.D.
Thomas A. Ullman, M.D.
Richard P. Wedeen, M.D.
Klaudiusz R. Weiss, Ph.D.

Editorial Board

Barry S. Coller, M.D.
Kenneth L. Davis, M.D.
Panayotis G. Katsoyannis, Ph.D.
Jack G. Rabinowitz, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, Septem October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-6 Subscription price: individuals (U.S. and Canada), $79 per year; libraries and institutions (U.S. and Canada), $121 per year; individuals (out U.S. and Canada), $105 per year; libraries and institutions (outside U.S. and Canada), $147 per year. The charge per copy of a single nun issue is $25, for a two-number issue is $50. New subscriptions begin with the first issue of the calendar year. Send notice of change of add 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send adc changes to *The Mount Sinai Journal of Medicine*, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212) 6108. Fax (212) 722-6386. e-mail: msjournal@mssm.edu; web page: www.mssm.edu/msjournal. Copyright 2003.

DISCLAIMER: The statements and opinions expressed in *The Journal* by authors and contributors are solely their own and not those of The Mount Medical Center or *The Mount Sinai Journal of Medicine*. All advertisements are expected to conform to ethical standards, and their appearance does not i endorsement or approval by The Mount Sinai Medical Center and/or *The Mount Sinai Journal of Medicine* of the products with respect to effectiveness, quali safety. The Mount Sinai Medical Center and *The Mount Sinai Journal of Medicine* do not hold themselves responsible for statements made by the auth contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in *The Journal* is protected by copyright. In accord with U.S. Copyright law, no part of *The Journal* may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior writ permission to do so. Permission should be requested from The Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 109 One East 100th Street, New York NY 10029-6574.

Grand Rounds

Gender Differences in Pulmonary Disease

CYNTHIA F. CARACTA, M.D.

Abstract

Epidemiologic evidence points to gender-based differences in incidence, risk, histology, and pathogenesis of certain lung diseases in women as compared with men. Gender influences not only physiological differences, but also the social, economic, and cultural context in which men and women coexist. Central to these differences is the role of sex hormones, which may contribute to the pathogenesis of disease or serve as protective factors. This paper seeks to review the role of gender in major areas of pulmonary disease and explore the mechanisms that may underlie gender differences in asthma, chronic obstructive pulmonary disease and mycobacterial disease (tuberculosis and *Mycobacterium avium intracellulare* infection), on lung cancer.

Key Words: Antiestrogens, asthma, cigarette smoking, COPD, epidemiology, estrogens, lung cancer, mycobacteria, sex hormones, women.

Introduction

EPIDEMIOLOGIC EVIDENCE points to gender-based differences in the incidence, risk, histology, and pathogenesis of certain lung diseases in women as compared with men. Gender differences in asthma may be related to both cyclical and age-related changes in sex hormones, resulting in an age-related increase in asthma rate in females as compared with males, and to premenstrual asthma (PMA) syndrome, and fluctuations of asthma symptoms during pregnancy. However, the effects of postmenopausal use of hormone replacement therapy (HRT) on asthma are unclear. Gender-related differences in chronic obstructive pulmonary disease (COPD) may include an increased genetic susceptibility to tobacco smoke in women, which may be responsible for the observed decrease in lung function and increase in rate of hospitalization and mortality for COPD in women as compared with men. Gender differences in mycobacterial disease also exist, with females having increased prevalence of infection and clinical progression of disease as compared with males. In lung cancer, there is an increase in the incidence of both smoking- and nonsmoking-related lung tumors in women and an increased relative risk of lung cancer in women as compared with men. In addition, gender-related differences in the histology, etiologies, clinical presentations, therapy, and molecular oncogenesis of lung cancer exist.

Gender influences not only physiological differences, but also the social, economic, and cultural context in which diseases occur. Perhaps central to these differences is the role of sex hormones, which may contribute to the pathogenesis of disease or serve as protective factors. This paper seeks to review the role of gender in major areas of pulmonary disease and explore the mechanisms that may underlie these differences.

Gender and Asthma

The importance of asthma as a cause of chronic respiratory disease, whether it begins in

---

From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Cynthia F. Caracta, M.D., F.C.C.P., Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Box 1232, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; E-mail: Cynthia.Caracta@msnyuhealth.org

Based on a Grand Rounds presentation of the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY on October 2, 2001, and updated February 2003.

childhood, adolescence, or adulthood, is reflected in its increasing prevalence, morbidity, and mortality (1). Gender differences in asthma prevalence and severity vary by age and may be attributed to differences in biologic susceptibility due to changes in hormonal milieu with aging, environmental exposures, and health care accessibility (2). Asthma and wheezing are more common in prepubertal boys, and the odds ratio (OR) for asthma for boys between the ages 2 to 5 is 1.8 compared to girls. By age 14, the risk of chronic asthma is 4 times greater for boys and the risk of hospitalization is 3 times greater as compared to girls (2, 3). This difference may be attributed to boys' relatively smaller airway size and caliber as compared to girls at this age (4).

By age twenty there is a reversal of this incidence and a distinct female predominance in asthma: the OR for hospitalization is 2.5 to 3.0 for females as compared to males (2, 5 – 10). In addition, there is a greater prevalence of atopy in female asthmatics, increased bronchial responsiveness in women, and longer duration of hospitalization and morbidity with age in women (2, 5 – 10). To some extent, this reversal may be related to smaller relative airway caliber in women vs. men after puberty, but other factors may contribute, including changes in hormonal status occurring naturally with aging, differences in environmental/occupational exposures, and differences in quality of and access to health care, management of asthma, or perception of disease (2, 11).

Asthma severity may vary with short-term reproductive processes, including the menstrual cycle and pregnancy, and major female sex hormones such as progesterone and estrogen may play roles (12 – 19). As many as 40% of asthmatic females report premenstrual asthma (PMA). In normal menstruating subjects without asthma, lymphocyte β_2 adrenoreceptors are upregulated. During the luteal phase, serum progesterone levels decline just before menstruation. In menstruating subjects with asthma, this cyclical upregulation is absent (20, 21). Thus, the cyclical fluctuations in asthma symptoms may be related to the loss of upregulation of the β_2 adrenoreceptors and increased airway responsiveness to adenosine monophosphate (20 – 24). The reduction in premenstrual serum estrogen levels may also play a role, and it has been suggested that exogenous administration of estrogen may improve peak expiratory flow rate (PEFR) and attenuate symptoms (25). In premenopausal female asthmatics unresponsive to standard steroid therapy, hormone replacement therapy (HRT) may increase forced expiratory volume in one second (FEV_1) (26). Oral contraceptive pills (OCP), both combined estrogen-progestin and unopposed estrogen forms, may reduce dynamic fluctuations in patients with PMA and decrease menses-associated asthma (26). Furthermore, oral contraceptive users are found to have significantly higher total lung capacities when compared with nonusers during the follicular phase of the menstrual cycle and both combined estrogen/progesterone and unopposed estrogen forms of HRT may be associated with higher (FEV_1) in elderly postmenopausal females as compared to nonusers (26).

Results of studies addressing the effect of pregnancy on asthma are conflicting; discordant results may be due to differences in methodology and outcomes measured (19). Clinical studies suggest that asthma improves in one-third of pregnant women, worsens in one- third, and is unaffected in the remaining third (18, 19). According to some studies, women with more severe corticosteroid-dependent disease experience more exacerbations, especially during late pregnancy, while other studies suggest that symptoms abate during the third trimester and that 26 – 40% experience an increase in asthma symptoms post partum (18, 19). Reasons for these clinical observations are thought to be depressed T-cell function and changes in levels of sex hormones, other steroid hormones and pregnancy-related anti-inflammatory factors.

Among studies addressing how changes in hormonal status with aging and the postmenopausal use of HRT affect asthma, conclusions are divided. Use of unopposed estrogen was associated with reduced airway reactivity to histamine challenge in postmenopausal nonsmoking women without pulmonary disease. Those taking estrogen showed a lower maximal decrease in FEV_1 after bronchopulmonary challenge compared to nonusers, suggesting that estrogen replacement may have an inhibitory effect on bronchial reactivity (27). For a cohort of 2,353 women over age 65, in the Cardiovascular Heart Study, overall HRT use was significantly associated with lower prevalence of obstruction. However, a different conclusion was reached in the Nurses Health Study, in which postmenopausal women using HRT for ten years or more had twice the age-adjusted risk of developing asthma when compared to postmenopausal women not using HRT (28). Self-report questionnaires in the Copenhagen City

Heart Study showed only a weak association between HRT and self-reported asthma, but found that in premenopausal women, use of oral contraceptive pills was associated with a greater prevalence of asthma (6.2%) as compared to nonusers (4.8%) (29). *In vitro* estrogens are shown to possess anti-inflammatory properties, and in healthy postmenopausal women the administration of estradiol reduces the skin-delayed immune responses and mixed lymphocyte reactions; estradiol and progesterone reduce the oxidative capacity induced by phagocytic stimulus and inhibit neutrophil degranulation; and estrogen and progesterone receptors are overexpressed in the human allergic mucosa and occur mainly on activated eosinophils (17). These observations may suggest the underlying mechanisms for a protective effect of estrogens on respiratory function, while the reasons these hormones may predispose to pulmonary disease are unclear.

Gender and Chronic Obstructive Pulmonary Disease

In 1997, chronic obstructive pulmonary disease (COPD) was the fourth largest cause of death in the U.S., after cardiovascular disease, cerebral vascular disease, and tumors, and in 2020, COPD is expected to become the third largest cause of death worldwide (30). Risk factors have been thought to include age, male gender, smoking/air pollution, occupational exposures, and lower socioeconomic status (30). COPD is believed to be more prevalent among men than women, due to higher smoking rates in men and their occupational exposures; however, with the increase in smoking among women and their entrance into the workforce, these demographic differences are disappearing. Moreover, there is evidence that women are more susceptible to smoking-related COPD than are men, having increased rate of decline of lung function associated with COPD, and increased COPD-related morbidity and mortality (30–35). Gender bias may also underestimate the rates of COPD in women, as shown in one study (36), in which physician rates of diagnosis of asthma vs. COPD were gender-dependent. In this study, a single hypothetical case presentation consistent with COPD was presented to 192 primary care physicians and assigned either to a female or male patient. If the patient was presented as a female, physicians were more likely to diagnose asthma, and the male patient was more likely to be diagnosed with COPD (58% vs. 42% of the time). The likelihood of a COPD diagnosis increased significantly and initial differences between the sexes decreased as objective information was provided, but only 22% of the physicians would have requested spirometry after the initial presentation. The authors concluded that in North America, primary-care physicians underdiagnose COPD in women and that spirometry, though underutilized, reduces the risk of underdiagnosis and gender bias (36).

Gender and Mycobacterial Disease

Tuberculosis (TB) is a global problem, particularly in developing countries, where it is the third most common cause of morbidity and mortality combined and kills more women than any other infectious disease, including malaria and AIDS (37). TB kills more than one million women per year, and 646 million women and girls are infected globally (37). Epidemiological studies note differences in prevalence of infection, rate of progression, incidence of clinical disease and mortality between men and women. Women have a higher progression rate from infection to disease and a higher case-fatality rate (38, 39). Prevalence studies indicate that males are more likely to exhibit positive skin tuberculin tests and that fewer females are smear-positive on sputum sampling as compared to males (38, 39). Differences in immune responses may account for the differences in signs, symptoms, forms, and outcomes of TB in women as compared with men. In addition, sex and non-sex steroid hormones may play a role in these observed differences, as they may with asthma. Social, economic, and cultural factors may also contribute, since 70% of the world's poor are female, with limited access to health care. Other gender disparities, including delayed diagnosis and differences in attitudes of female vs. male patients and of physicians themselves toward TB, are also recognized as important factors (40–45).

Pulmonary disease due to *Mycobacterium avium intracellulare* (MAI) is no longer a disease limited to elderly men with chronic bronchitis and COPD, inactive or active TB, bronchiectasis, pneumoconiosis, chronic aspiration pneumonia, bronchogenic carcinoma and to those with deficient cellular immunity or who are recovering from immunosuppressive drugs. Post-gastrectomy patients are also at risk for pulmonary MAI infection. Disseminated disease in patients with challenged cellular immunity is typified by MAI in patients with AIDS. However, recent series show that 81–94% of patients identified with pulmonary MAI in immunocompetent adults were female, with a mean age range of 60–66 (46–52). "The Lady Windemere's syndrome" was coined after these observations, to describe a syndrome of chronic cough, weight loss, fatigue, fever/night sweats, and hemoptysis in an immunocompetent, elderly, white female nonsmoker with bronchiectasis and nodular disease on computed tomography of the chest (49). A subtle immune defect, which is either acquired or a genetic allelism (e.g., NRAMP1 and interferon-gammaR1), as well as hormonal differences (e.g., declining estrogen levels) have been implicated as mechanisms that result in this apparent gender predilection (53, 54). There is no apparent gender difference in populations of AIDS patients with MAI (55).

Gender and Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disease occurring exclusively in women. It mainly affects premenopausal women and is characterized by smooth muscle cell proliferation, primarily in the lung and extrapulmonary sites such as lower cervical, thoracic, abdominal and pelvic lymph nodes (56–59). Atypical smooth muscle proliferation and infiltration lead to progressive loss of lung function, resulting in the two most common presenting symptoms of dyspnea and pneumothorax. The pathologic findings in LAM are identical to those in tuberous sclerosis involving the lung. Interestingly, as in tuberous sclerosis, there is an association of LAM with renal angiomyolipoma. While there is no direct evidence that LAM is an inherited disorder, as is tuberous sclerosis, many investigators have suggested that LAM may be closely related to or a *forme fruste* of tuberous sclerosis. Such a relationship remains unclear (56).

The involvement of female sex hormones in the pathogenesis of LAM is suggested by the occurrence of LAM in premenopausal women during their childbearing years and the development of symptoms or increase in the extent of the symptoms during pregnancy. Cases of the disease or progression of the disease following exogenous estrogen administration have been reported, but no association has been found between the use of oral contraceptives and LAM (56). While no specific laboratory abnormalities have been reported in patients with LAM, estrogen and progesterone receptors have been found in proliferating LAM cells and not in normal smooth muscle cells in the lungs of LAM patients, thus suggesting that sex hormones may play a role in the pathogenesis of LAM (56–58). The occurrence of disease in premenopausal women, reports of worsening with exogenous estrogen, and the presence of estrogen and progesterone receptors in LAM cells provided a rationale for hormonal manipulation as therapy. Currently, patients with LAM are being treated with oophorectomy/radioablation of the ovaries, progesterone, tamoxifen, luteinizing-hormone-releasing agonists, and other antiestrogens (56, 59–61), although the efficacy of these treatments has not been proven. In addition to hormonal involvement, tumor-suppressor genes found in tuberous sclerosis may be involved, given the similarities of disease phenotypes between LAM and tuberous sclerosis (56). Patients with end-stage LAM who underwent bilateral lung transplant have had recurrence of disease in the male donor lungs, suggesting the theory that a circulating factor or mitogen may be involved (56). Whether this mitogen is a sex hormone or the product of imbalances in tumor-suppressor genes is unknown, but given current epidemiological evidence, the pathway to LAM appears to be gender-associated.

An interesting empirical observation is that HMB-45 immunostains lung tissue in a significant number of cases of LAM. HMB-45 is a mouse monoclonal antibody against proteins produced by melanoma cells. The reason for this association is unknown (personal communication, Dr. Joan Gil, November 26, 2002).

Gender and Lung Cancer

Gender Influences on the Epidemiology of Lung Cancer

Worldwide, lung cancer is the most frequent cancer, accounting for 12% of all new cancer diagnoses in both sexes combined (62). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program suggest a projection of 164,100 new cases in the U.S. in the year 2000, 89,500 males and 74,600 females, with 89,300 new deaths for men and 67,600 for women (63). Since 1950, lung cancer rates have increased by 500% in women, and from 1960–1980 lung cancer death rate ratios in smokers as compared to nonsmokers rose from 12 to 22 in men (1.8-fold increase), and from 3 to 11 in women (3.6-fold increase) (64, 65). In 1986, lung cancer surpassed breast cancer as the leading cause of female cancer-related deaths. Currently, 21% of the American female population smoke, and for the same level of smoking, the relative risk of non-small-cell lung cancer is 1.7 to 2.9 compared to men (66, 67). Women may also have a higher OR than men for small-cell lung cancer (68–70).

Gender Differences in Lung Cancer Histology

In addition to the above data, the histology of lung cancer indicates gender differences. In the 1980s, adenocarcinoma surpassed squamous cell as the major type of lung cancer (71). SEER data from 1973–1994 reported that the relative risk for women for adenocarcinoma of the lung increased from 1.5 to 8.1, and that for men it increased from 4.6 to 19.0 (72). Between 1973 and 1992, patients younger than 50 presented with more cases of advanced disease, and although there were no significant differences with regard to overall survival, time to progression, or role of smoking status, a surprisingly higher percentage of younger patients were female (45%). Moreover, 26% of these have never been smokers, suggesting that factors other than smoking may contribute to the pathology of lung adenocarcinoma in women (73, 74). Women appear more likely to present with adenocarcinoma. Studies on tumor progression in 3,312 registered Japanese lung cancer patients between 1977 and 1996 showed that only 3.9% of the women were smokers and that 73.6% had adenocarcinoma. Of the 2,369 men, 95% were smokers and only 42% had adenocarcinoma histologically. The odds ratio for advanced disease and the hazard ratio for survival were higher for women with adenocarcinoma than for those with other types of lung cancer, and closely correlated with smoking history. This association was not observed in women with non-adenocarcinoma histological subtypes and was weaker in men, suggesting that the various effects of smoking on lung cancer development depend on gender and histological type of tumor (75).

Etiologies and Factors in Lung Cancer

Factors linked to lung cancer in women include those with environmental, social, and behavioral bases. Environmental factors include: smoking, radon, arsenic, asbestos, chromium, nickel, silica, coal/cooking oils, air pollution, and petrochemicals. Many social/behavioral factors are recognized. As compared to men who have quit smoking, women are observed to have worse relapse rates; this may be a result of physiological differences such as gender-related responses to nicotine, sensation of satiety/withdrawal, heart rate and muscle tension perception, as well as differences in perception of weight loss control, lower expectations of ability to quit, and higher rates of depression (76). On the other hand, women do appear to be more likely to ask for cessation assistance (76). Specific risk factors for smoking in teenage girls are linked to lower educational goals/socioeconomic status, in which there are no plans for higher education or college degree; the level of parent education; high school dropout status; and single parenthood girls (77).

Risk factors for malignancy were reported as part of a study of 1,000 volunteers aged 60 and older with a minimum of 10 pack/year smoking history enrolled in early lung cancer screening by low-dose computed tomography; 46% of those enrolled were women. Nineteen out of the 29 tumors occurred in women, with a prevalence of 4.1 vs. 1.8% in men. Only two significant predictors of the probability of malignancy were reported in this pilot study: nodule size and female gender (78). The increase in the number of teenage girls smoking provides another population at growing risk and a source of increasing incidence in lung cancer in women over time.

Gender Differences in Clinical Observations in Lung Cancer

There may be gender-associated differences in presentation, therapy, and prognosis of non-small-cell lung cancer (NSCLC). A retrospective study of 208 cases of NSCLC showed that men present with pain, hemoptysis, and cough, while women present with pain, cough and dyspnea. There were no differences in stage of presentation, therapy, or survival advantage (79). In similar studies, women tended to be younger, more asymptomatic and non-to-light smokers, had more adenocarcinoma vs. squamous histology and stage 1 presentation, and tended to have a small survival advantage (80–82). No significant differences in therapy or operative mortality were noted; however, bronchoscopies were done in 90% of men vs. 80% of women and contributed to the preoperative diagnosis in

69% of men vs. 49% of women, while fine-needle aspiration with fluoroscopy was done in 17% women vs. 7% in men. Women had fewer (22% vs. 32%) pneumonectomies than did men (82).

Gender and Oncogenesis in Lung Cancer

While smoking is a major risk factor for lung cancer, only 10% of heavy smokers will get lung cancer and 10% of all cases of lung cancer are found in nonsmokers (83, 84). Early familial aggregation studies have shown evidence of genetic influence (76). Lung cancer itself represents the interaction between exposure to environmental mutagens and the genetic susceptibility to molecular alterations. These molecular alterations are thought to occur in stepwise fashion over several years, resulting in lung cancer in a small group of susceptible individuals in whom the initiating insult (e.g., cigarette smoke) causes multiple molecular alterations via different pathways (85). Genetic susceptibility or predisposed risk may arise because of differences in levels of enzymes such as glutathione S-transferase and the activity of cytochrome p450 pathways which may alter detoxification of carcinogens and carcinogenic metabolites. These metabolites may directly interact with and bind to DNA, resulting in DNA adduct formation. There is evidence that women are more susceptible to tobacco-associated DNA adduct formation. DNA adducts in peripheral blood leukocytes and normal lung tissues of patients with lung cancer are higher in females for all levels of smoking compared to men, and levels of adducts have correlated with cancer risk (85–87).

If there is failure in DNA repair, persistence of mutations and accumulation of mutations may ultimately lead to lung cancer. Other pathways that may be affected by mutations that result in alterations in the normal cell growth cycle which favor cellular proliferation over normal cellular senescence or apoptosis (88). While the prevalence of smoking and the increase in smoking trends among women may account for part of the increased incidence of lung cancer in women, a growing number of molecular studies also suggest that women smokers and nonsmokers are more susceptible to lung cancer than are their male counterparts.

Gender and Oncogenic Mutations

Glutathione-S-transferase M1 (GSTM1), thought to be a cancer susceptibility marker, catalyzes the metabolic detoxification of polycyclic aromatic hydrocarbons (PAHs) styrene and ethylene oxides in cigarette smoke. Its associated gene is absent in 40–50% of the U.S. population, and this homozygous deletion can lead to an increased incidence of PAH adducts and mutagenicity. The OR for lung cancer is 3 in female smokers vs. 1.4 in male smokers (89). Among never-smoking females exposed to environmental tobacco smoke (ETS), those who developed lung cancer were more likely to be deficient in GSTM1 activity, with an OR of 2.6 as compared to those without ETS exposure (90). These data support the theory of increased genetic susceptibility of women to the effects of tobacco carcinogens as compared to men, and that polymorphisms play a role in the pathogenesis of lung cancer in passive-smoking exposures in women.

K-*ras* is the proto-oncogene in which most mutations occur in smokers, with 80–90% occurring in codon 12 and G to T transversions. Wang et al. (91) studied K-*ras* mutations in 84 Taiwanese women, predominantly nonsmokers with resected stage I adenocarcinomas for K-*ras* mutations, and found that only 6% had mutations, with 4 out of 5 occurring in codon 12 or 13. All mutations found in males occurred in smokers, suggesting a difference in lung cancer pathogenesis between men and women in this population of patients. Nelson et al. (92) examined the role of gender in smoking and survival as they related to K-*ras* mutations in patients with adenocarcinoma of the lung. K-*ras* mutation was associated with adenocarcinoma of the lung only in smokers and was more likely to be found in women than in men, with an OR of 3.3, suggesting an increased female susceptibility to this mutation and to the effects of smoking. However, decreased survival was only noted for stage I tumors. These two studies of different populations appear to support an overall increase in K-*ras* in smoking women, which may be caused by an increased susceptibility to the effects of tobacco smoke in women. The studies also suggest that the pathogenesis of adenocarcinoma in nonsmoking men and women may occur by different pathways.

p53 is a tumor-suppressor gene in which mutations occur in guanine/cytodine base pairs in regions between exons 4 and 9. Hotspots include codons 157–158, 179, 245–249, 273, and 282. Kure et al. report an increase in p53 mutations in females vs. males with NSCLC (93), while another study reports that the frequency of p53 mutations is similar for smoking men and women, but the mutations are different

(94). In the latter study, K-*ras* mutations in smoking women were increased in women with lung cancer, but were identical to those occurring in men. Tseng et al. (95) examined p53 in 37 females and 28 males with small-cell lung cancer and noted fewer mutations in p53 in women vs. men. None of the females had more than one mutation, whereas four of the males had more than one. The most common mutations in women were adenosine to guanine in 27%, 17% guanine to thymidine and 12% guanine to adenosine, suggesting that pathways in small-cell lung cancer in women may not involve p53 as frequently as they do in men.

Gender and Trophic Influences in Lung Cancer

Gastrin-releasing peptide receptor (GRPR) is a bombesin-like peptide and autocrine growth factor gene located on xp22.3-p21. It can cause growth stimulation in lung cancers and is mediated through a family of G-protein-coupled bombesin receptors such as GRPR, neuromedin B receptor, and bombesin receptor subtype 3. It escapes inactivation in females and may be activated earlier in females in response to tobacco exposure. The presence of two expressed copies of the gene may be a factor in women's increasing susceptibility to lung cancer. Increased expression of the receptor in females for all levels of smoking has been reported, with increased expression of GRPR mRNA found in lung tissue and cultured cells from 40 males and 38 females, suggesting either gene duplication or increased transcription. Expression was highest in female nonsmokers and short-term smokers in women vs. men (96).

A hormonal factor, i.e., estrogen, is postulated as a reason for increased susceptibility to lung cancer in women. Animal studies show increased incidence of pulmonary neoplasms in animals receiving estrogen (97). Women receiving exogenous estrogen replacement therapy have increased risk of adenocarcinoma of the lung as compared to patients with early menopause, and this risk is additive with smoking (98). Estrogen-dependent cancer models such as those of the breast and the endometrium have been well studied. With the finding of the estrogen receptor alpha and beta in both normal and lung tumor tissues by immunohistochemistry, affinity binding, and reverse transcription polymerase chain reaction (RT-PCR), it now seems that estrogen may play a role in the pathogenesis of lung cancer and that it may account for the increased incidence in women. However, the role of estrogen in lung cancer still remains unclear (99). Estrogen may play a biological role in lung cancer growth stimulation in cancers expressing the receptors. With the discovery of the estrogen receptor (ER) beta and multiple functional isoforms, and since studies suggest important functional differences between ER alpha and beta, it is possible that different receptor types or forms of the estrogen receptor may play different roles in the pathogenesis of lung cancer. This possibility provides a rationale for novel therapies for certain lung cancers with antiestrogens (99). Tamoxifen induces apoptosis and blocks estrogen-induced cellular proliferation of lung tumor cell lines *in vitro*. Clinical studies involving phase II trials of tamoxifen as adjuvant therapy in advanced NSCLC showed acceptable toxicity and favorable response rate and survival times in patients who received conventional therapy and tamoxifen (100–103).

Conclusion

Epidemiologic and molecular evidence points to women's susceptibility to lung cancer, and gender differences in pulmonary diseases not generally restricted to or typical of women. These physiological differences may provide important clues to the prevention, diagnosis, and treatment of pulmonary disease in women, but differences in social, economic and cultural contexts in which both men and women exist must also be considered when addressing both women's and men's health issues.

References

1. Guidelines for the Management of Asthma. National asthma educational project. Expert panel report. U.S. Dept. of Health and Human Services. 1991. Publication 91-3042.
2. Redline S, Gold D. Challenges in interpreting gender differences in asthma. Am J Respir Crit Care Med 1994; 150(5 Pt 1):1219–1221.
3. Bjornson CL, Mitchell I. Gender differences in asthma in childhood and adolescence. J Gender Specific Med 2000; 3(8):57–61.
4. Becklake MR, Kauffman F. Gender differences in airway behaviour over the human life span. Thorax 1999; 54:1119–1138.
5. Paoletti P, Carrozzi L, Viegi G, et al. Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. Am J Respir Crit Care Med 1995; 151:1779–1777.
6. Prescott E, Lange P, Vestbo J. Effect of gender on hospital admissions for asthma and prevalence of self-reported asthma: a prospective study based on a sample of the general population. The Copenhagen City Heart Study Group. Thorax 1997; 52(3):287–289.

7. Gustafsson PM, Kjellman B. Asthma from childhood to adulthood: course and outcome of lung function. Respir Med 2000; 94:466–474.
8. Kjellman B, Gustafsson PM. Asthma from childhood to adulthood: asthma severity, allergies, sensitization, living conditions, gender influence and social consequences. Respir Med 2000; 94:454–465.
9. Fagan JK, Scheff PA, Hryhorczuk D, et al. Prevalence of asthma and other allergic diseases in an adolescent population: association with gender and race. Ann Allergy Asthma Immunol 20001; 86(2):177–184.
10. Trawick DR, Holm C, Wirth J. Influence of gender on rates of hospitalization, hospital course, and hypercapnea in high-risk patients admitted for asthma: a 10-year retrospective study at Yale-New Haven Hospital. Chest 2001; 1:115–119.
11. Osborne ML, Vollmer WM, Linton KL, Buist AS. Characteristics of patients with asthma within a large HMO. Am J Respir Crit Care Med 1998; 157:123–128.
12. Hanley SP. Asthma variation with menstruation. Br J Dis Chest 1981; 75:306–308.
13. Gibbs CJ, Coutts II, Lock R, et al. Premenstrual exacerbation of asthma. Thorax 1984; 39:833–836.
14. Eliasson O, Scherzer HH, DeGraff AC, Jr. Morbidity in asthma in relation to the menstrual cycle. J Allergy Clin Immunol 1986; 77:87–94.
15. Perrin B, Bousquet J, Michel FB, et al. Severe premenstrual asthma. Lancet 1988; 833–834.
16. Pauli BD, Reid RL, Munt PW, et al. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. Am Rev Respir Dis 1989; 140:358–362.
17. Balzano G, Fuschillo S, Melillo G, Bonini S. Asthma and sex hormones. Allergy 2001; 56:13–20.
18. Tan KS, Thomson NC. Review: asthma in pregnancy. Am J Med 2000; 109:727–733.
19. Nelson-Piercy C. Asthma in pregnancy. Thorax 2001; 56:325–328.
20. Juniper EF, Kline RS, Roberts FE, et al. Airway responsiveness to methacholine during the natural menstrual cycle and the effect of oral contraceptives. Am Rev Respir Dis 1987; 135:1039–1042.
21. Tan KS. Premenstrual asthma: epidemiology, pathogenesis, and treatment. Drugs 2001; 6(14):2079–2086.
22. Tan SK, McFarlane LC, Lipworth BJ. Paradoxical down-regulation and desensitization of β2- adrenoreceptors by exogenous progesterone in female asthmatics. Chest 1997; 111:847–851.
23. Tan KS, McFarlane LC, Lipworth BJ. Loss of normal cyclical β2-adrenoreceptor regulation and increased premenstrual responsiveness to adenosine monophosphate in stable female asthmatic patients. Thorax 1997; 52:608–611.
24. Tan KS, McFarlane LC, Lipworth BJ. β2-adrenoreceptor regulation and function in female asthmatic patients receiving the oral combined contraceptive pill. Chest 1998; 113:278–282.
25. Chandler MH, Schuldheisz S, Phillips BA, Muse KN. Premenstrual asthma: the effect of estrogen on symptoms, pulmonary function, and beta-2-receptors. Pharmacotherapy 1997; 17(2):224–234.
26. Carlson CL, Cushman M, Enright PL, et al. Hormone replacement therapy is associated with higher FEV1 in elderly women. Am J Resp Crit Care Med 2001; 163:423–428.
27 Lieberman D, Kopernic F, Porath G, et al. Influence of estrogen replacement therapy on airway reactivity. Respiration 1995; 62:205–208.
28. Troisi RJ, Speizer FE, Willett WC, et al. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. Am J Respir Crit Care Med 1995; 152: 1183–1188.
29. Lange P, Parner J, Prescott E, et al. Exogenous female sex steroid hormones and risk of asthma and asthma-like symptoms: a cross sectional study of the general population. Thorax 2001; 56:613–616.
30. Viegi G, Scognamilio A, Baldacci S, et al. Epidemiology of chronic obstructive pulmonary disease (COPD). Respiration 2001; 68(1):4–19.
31. Silverman EK, Weiss ST, Drazen JM, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 162:2152–2158.
32. Kanner RE, Connett JE, Altose MD, et al. Gender difference in airway hyperresponsiveness in smokers with mild COPD: the Lung Health Study. Am J Respir Crit Care Med 1994; 150:956–961.
33. Prescott E, Bjerg AM, Andersen PK, et al. Gender difference in smoking effects on lung function and risk of hospitalization of COPD: results from a Danish longitudinal populational study. Eur Respir J 1997; 10(4):822–827.
34. Nilsson S, Carstensen JM, Pershagen G. Mortality among male and female smokers in Sweden: a 33-year follow-up. J Epidemiol Community Health 2001; 55:825–830.
35. Mannino DM. COPD: epidemiology, prevalence, morbidity, and mortality, and disease heterogeneity. Chest 2002; 121:121S–126S.
36. Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. Chest 2001: 119:1691–1695.
37. Diwan VK, Thorson A. Sex, gender, and tuberculosis. Lancet 1999; 353(9157):1000–1001.
38. Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. Int J Tuberc Lung Dis 1998; 2:96–104.
39. Boeree MJ, Harries AD, Godschalk P, et al. Gender differences in relation to sputum submission and smear-positive pulmonary tuberculosis in Malawi. Int J Tuberc Lung Dis 2000; 4(9):882–884.
40. Thorson A, Diwan VK. Gender inequalities in tuberculosis: aspects of infection, notification rates, and compliance. Curr Opin Pulm Med 2001; 7(3):165–169.
41. Cegielski JP, Goetz MB, Jacobson JM, et al. Gender differences in early suspicion of tuberculosis in hospitalized, high-risk patients during 4 epidemic years, 1987 to 1990. Infect Control Hosp Epidemiol 1997; 18(4):237–243.
42. Uplekar MW, Rangan S, Weiss MG, et al. Attention to gender issues in tuberculosis control. Int J Tuberc Lung Dis 2001; 5(3):220–224.
43. Hudelson P. Gender differentials in tuberculosis: the role of socio-economic and cultural factors. Tuber Lung Dis 1996; 77(5):391–400.
44. Long NH, Johansson E, Diwan VK, Winkvist A. Fear and social isolation as consequences of tuberculosis in Vietnam: a gender analysis. Health Policy 2001; 58(1):69–81.
45. Begum V, de Colombani P, Das Gupta S, et al. Tuberculosis and patient gender in Bangladesh: sex differences in diagnosis and treatment outcome. Int J Tuberc Lung Dis 2001; 5(7):604–610.
46. Prince DS, Peterson DD, Steiner RM, et al. Infection with Mycobacterium avium complex in patients without predisposing conditions. N Engl J Med 1989; 321(13):863–868.
47. Kubo K, Yamazaki Y, Hachiya T, et al. Mycobacterium avium-intracellulare pulmonary infection in patients without known predisposing lung disease. Lung 1998; 176:381–391.
48. Hartman TE, Swensen SJ, Williams DE. Mycobacterium avium-intracellulare complex: evaluation with CT. Radiology 1993; 187(1):23–26.
49. Teirstein AS, Damsker B, Kirschner PA, et al. Pulmonary infection with mycobacterium avium-intracellulare: diagnosis, clinical patterns, treatment. Mt Sinai J Med 1990; 57(4):209–215.

50. Reich JM, Johnson RE. Mycobacterium avium complex pulmonary disease presenting with isolated lingular or middle lobe pattern. The Lady Windermere syndrome. Chest 1992; 101(6):1605–1609.

51. Huang JH, Kao PN, Adi V, et al. Mycobacterium avium-intracellulare pulmonary infection in HIV-negative patients without preexisting lung disease. Chest 1999; 115:1033–1040.

52. Huang JH, Hefner PJ, Adi V, et al. Analyses of the NRAMP1 and INF-γR1 genes in women with mycobacterium avium intracellulare pulmonary disease. Am J Respir Crit Care Med 1998; 157:377–381.

53. Kubo K, Yamazaki Y, Hanaoka M, et al. Analysis of HLA antigens in Mycobacterium avium-intracellulare pulmonary infection. Am J Respir Crit Care Med 2000; 161(4 Pt 1):1368–1371.

54. Tsuyuguchi K, Suzuki K, Matsumoto E, et al. Effect of oestrogen on Mycobacterium avium complex pulmonary infection in mice. Clin Exp Immunol 2001; 123:428–434.

55. Benson CA. Disease due to the Mycobacterium avium complex in patients with AIDS: epidemiology and clinical syndrome. Clin Infect Dis 1994; 18:S218–S222.

56. Sullivan, EJ. Lymphangioleiomyomatosis: a review. Chest 1998; 114:1689–1703.

57. Berger U, Khaghani A, Pomerance A, et al. Pulmonary lymphangioleiomyomatosis and steroid receptors. An immunocytochemical study. Am J Clin Pathol 1990; 93(5):609–614.

58. Colley MH, Geppert E, Franklin WA. Immunohistochemical detection of steroid receptors in a case of pulmonary lymphangioleiomyomatosis. Am J Surg Pathol 1989; 13(9):803–807.

59. Matsui K, Tatsuguchi A, Valencia J, et al. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. Hum Pathol 2000; 31(10):1242–1248.

60. Ferrans VJ, Yu ZX, Nelson WK, et al. Lymphangioleiomyomatosis (LAM): a review of clinical and morphological features. J Nippon Med Sch 2000; 67(5):311–329.

61. Kelly J, Moss J. Lymphangioleiomyomatosis. Am J Med Sci 2001; 321(1):17–25.

62. Franceschi S, Bidoli E. The epidemiology of lung cancer. Ann Onc 1999; 10(Suppl 5):S3–S6.

63. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000; 50(1):7–33.

64. American Cancer Society. Cancer facts and figures — 1994. Atlanta, GA: American Cancer Society; 1994. pp. 1–28.

65. Thun MJ, Lally CA, Flannery JT, et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Instit 1997; 89(2):1580–1586.

66. Zang, EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Instit 1996; 88(3/4):183–192.

67. Risch HA, Howe GR, Jain M, et al. Are female smokers at higher risk for lung cancer than male smokers: a case-control analysis by histologic type. Am J Epidemiol 1993; 138:281–293.

68. Schoenberg JB, Wilcox HB, Mason TJ, et al. Variation in smoking-related lung cancer risk among New Jersey women. Am J Epidemiol 1989; 130:688–695.

69. Brownson RC, Chang JC, Davis JR. Gender and histologic type variations in smoking- related risk of lung cancer. Epidemiology 1992; 3:61–64.

70. Osann KE, Anton-Culver H, Kurosaki T, Taylor T. Sex differences in lung-cancer risk associated with cigarette smoking. Int J Cancer 1993; 54:44–58.

71. Charloux A, Quoix E, Wolkove N, et al. The increasing incidence of lung adenocarcinoma: reality or artifact? A review of the epidemiology of lung adenocarcinoma. Int J Epidemiol 1997; 26:14–23.

72. Travis WD, Travis LB, Devessa SS. Lung cancer. Cancer 1995; 75:191–202.

73. Liu N, Spitz MR, Kemp BL, et al. Adenocarcinoma of the lung in young patients. The M.D. Anderson Experience. Cancer 2000; 88:1837–1841.

74. Morgan LC, Grayson D, Peter HE, et al. Lung cancer in New South Wales: current trends and influence of age and sex. Med J Aust 2000; 172(12):578–582.

75. Sekine I, Nagai K, Tsugane S, et al. Association between smoking and tumor progression in Japanese women with adenocarcinoma of the lung. Jpn J Cancer Res 1999; 90(2):129–135.

76. Ernster VL. Female lung cancer. Annu Rev Public Health 1996; 17:97–114.

77. U.S. Department of Health and Human Services 1994. Preventing tobacco use among young people: a report of the Surgeon General. Atlanta GA: US DHHS, Public Health Service, CDC, National Center of Chronic Diseases and Preventive Health Promotions.

78. Henschke CI, McCauley DI, Yanjekevitz DF, et al. Early lung cancer action project: overall design and findings from baseline screening. Lancet 1999; 354(9173):99–105.

79. Ouellette D, Desbiens G, Edmond, C, Beauchamp G. Lung cancer in women compared with men: stage, treatment, and survival. Ann Thor Surg 1998; 66:1140–1144.

80. Ferguson MK, Wang J, Hoffman PC, et al. Sex-associated differences in survival of patients undergoing resection for lung cancer. Ann Thorac Surg 2000; 69:245–250.

81. Bouchardy C, Fioretta G, De Perrot M, et al. Determinants of long term survival after surgery for cancer of the lung: a population-based study. Cancer 1999; 86:2229–2237.

82. De Perrot M, Licker M, Bouchardy C, et al. Sex differences in presentation, management, and prognosis of patients with non-small cell lung carcinoma. J Thorac Cardiovasc Surg 2000; 119:21–26.

83. Wingo PA, Reis LAG, Grovino GA, et al. Annual report to the nation on the status of cancer 1973–1996, with a special section on lung cancer and tobacco smoking. J Natl Cancer Instit 1999; 91(8):675–690.

84. Landis S, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999; 49:8–31.

85. Ryberg D, Hewer A, Phillips DH, Haugen A. Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. Cancer Res 1994; 54(22):5801–5803.

86. Mollerup S, Ryberg D, Hewer A, et al. Sex differences in Lung CYP1A1 expression and DNA adduct levels among lung cancer patients. Cancer Res 1999; 59:3317–3320.

87. Tang D, Santella RM, Blackwood AM, et al. A molecular epidemiological case-control study of lung cancer. Cancer Epidemiol Biomarkers Prev 1995; 4(4):341–346.

88. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 1999; 91:1194–1210.

89. Tang DL, Rundle A, Warburton D, et al. Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. Carcinogenesis 1998; 19(11):1949–1953.

90. Bennett WP, Alavanja MCR, Blomeke B, et al. Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. J Natl Cancer Inst 1999; 91:2009–2014.

91. Wang YC, Lee HS, Chen SK, et al. Analysis of K-ras gene mutations in lung carcinomas: correlation with gender, histological subtypes, and clinical outcome. J Cancer Res Clin Oncol 1998; 124(9):517–522.

92. Nelson HH, Christiani DC, Mark EJ, et al. Implications and prognostic value of K-ras mutation for early-stage lung cancer in women. J Natl Cancer Inst 1999; 91(23):2031–2038.

93. Kure EH, Ryberg D, Hewer A, et al. p53 mutations in lung tumours: relationship to gender and lung DNA adduct levels. Carcinogenesis 1996; 17(10):2201–2205.

94. Gealy R, Zhang L, Siegfried JM, et al. Comparison of mutations in the p53 and K-ras genes in lung carcinomas from smoking and nonsmoking women. Cancer Epidemiol Biomarkers Prev 1999; 8(4 Pt 1):297–302.

95. Tseng JE, Rodriguez M, Ro J, et al. Gender differences in p53 mutational status in small cell lung cancer. Cancer Res 1999; 59:5666–5670.

96. Shriver SP, Bourdeau HA, Gubish CT, et al. Sex-specific expression of gastrin-releasing peptide receptor: relationship to smoking history and risk of lung cancer. J Natl Cancer Inst 2000; 92(1):24–33.

97. Lupulescu A. Hormonal regulation of epidermal tumor development. J Invest Dermatol 1981; 77:186–195.

98. Taoili E, Wynder EL. Endocrine factors and adenocarcinoma of the lung in women [letter]. J Natl Cancer Inst 1994; 86:869–870.

99. Moore JT, McKee DD, Slenta-Kesler K, et al. Cloning and characterization of human estrogen receptor β isoforms. Biochem Biophys Res Commun 1998; 247:75–78.

100. Yeh KH, Cheng AL. High-dose tamoxifen reverses drug resistance to cisplatin and etoposide in a patient with advanced large cell carcinoma of lung. Anticancer Res 1997; 17:1341–1344.

101. Lara PN, Gandara DR, Wurz GT, et al. High-dose toremifine as a cisplatin modulator in metastatic non-small cell lung cancer: targeted plasma levels are achievable clinically. Cancer Chemother Pharmacol 1998; 42:504–508.

102. Yang CH, Cheng AL, Yeh KH, et al. High dose tamoxifen plus cisplatin and etoposide can be safely administered as first-line treatment to patients with advanced, inoperable nonsmall cell lung carcinoma. Favorable response rates and survival times were obtained. Cancer 1999; 86:415–420.

103. Chen YM, Perng RP, Yang KY, et al. A phase II trial of tamoxifen, ifosfamide, epirubicin, and cisplatin combination chemotherapy for inoperable non-small-cell lung cancer. Am J Clin Oncol 2000; 23(1):13–17.

Grand Rounds

Evolving Rationale for Angiotensin-Converting Enzyme Inhibition in Chronic Heart Failure

Anita Banerjee, M.D., Ashok Talreja, M.D., Edmund H. Sonnenblick, M.D., and Thierry H. LeJemtel, M.D.

Abstract

The rationale behind the use of angiotensin-converting enzyme (ACE) inhibitors has evolved considerably since their approval for the treatment of hypertension. The initial rationale behind their use for the treatment of chronic heart failure was to duplicate with one agent the hemodynamic effects produced by the hydralazine-isosorbide dinitrate combination, i.e., increasing cardiac output while reducing ventricular filling pressures. The observation that the acute hemodynamic effects of ACE inhibitors did not predict long-term clinical benefits led to the search for mechanisms other than hemodynamic improvement. Attenuation or even reversal of left ventricular dilatation after myocardial infarction, which was first reported with ACE inhibition in an experimental model of myocardial infarction and subsequently in patients with recent myocardial infarction, provided a new rationale for the use of these inhibitors for chronic heart failure. However, this apparent prevention of left ventricular dilatation by ACE inhibitors is less apparent in patients with congestive heart failure due to left ventricular systolic dysfunction (decreased ejection fraction) than in patients with recent myocardial infarction. Furthermore, the unexpected finding that long-term ACE inhibition decreases the incidence of recurrent myocardial infarction in patients with coronary artery disease and an already reduced systolic function, suggested the hypothesis that vascular protection may provide most of the clinical benefits of ACE inhibitors. This hypothesis was successfully tested by demonstrating a lower incidence of cardiovascular events in high-risk vascular patients randomized to long-term ACE inhibition with ramipril. Accordingly, the current rationale behind the use of ACE inhibitors in patients with chronic heart failure is largely that of vascular protection.

Key Words: Angiotensin-converting enzyme inhibition, left ventricular remodeling, vascular protection, chronic heart failure.

Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AIRE	Acute Infarction Ramipril Efficacy
CAD	coronary artery disease
CHF	chronic heart failure
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
EF	ejection faction
FDA	Food and Drug Administration
HOPE	Heart Outcome Prevention Evaluation
IMT	intimal medial thickness
LAD	left anterior descending
LV	left ventricular
LVED	left ventricular end diastolic
LVEF	left ventricular ejection faction
MI	myocardial infarction
NYHA	New York Heart Association
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
RAAS	renin-angiotensin-aldosterone system
SAVE	Survival and Ventricular Enlargement
SECURE	Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E

From the Department of Medicine, Albert Einstein College of Medicine, Bronx, NY.

Address all correspondence to Thierry H. LeJemtel, M.D., Albert Einstein College of Medicine, 1300 Morris Park Avenue, Forcheimer G44, Bronx, NY 10461; E-mail: lejemtel@aecom.yu.edu

Based on a Grand Rounds presentation of the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, NY on April 22, 2002, and updated in February 2003.

SOLVD	Studies of Left Ventricular Dysfunction
TIA	transient ischemic attack
TREND	Trial on Reversing Endothelial Dysfunction
V-HeFT	Vasodilators in Heart Failure Trial

Introduction

Long-term modulation of the renin-angiotensin-aldosterone system (RAAS) with inhibitors of the angiotensin-converting enzyme (ACE) is, along with beta-adrenergic blockade, the cornerstone of the pharmacological treatment of chronic heart failure (CHF) due to left ventricular (LV) systolic dysfunction characterized by a reduced ejection fraction (EF). The rationale for the use of ACE inhibitors in patients with cardiovascular disease has changed over the past 30 years. The initial impetus behind the use of ACE inhibitors for patients with CHF stems from the hemodynamic effectiveness of vasodilating agents. Nonspecific vasodilator agents such as nitroprusside, hydralazine or prazosin improve LV systolic performance, as evidenced by a rise in cardiac output at lower LV filling pressure (1). ACE inhibition with captopril was viewed as an attractive alternative to the combination of hydralazine and isosorbide dinitrate that was then used to reduce both preload and afterload (2–4). The lack of correlation between the acute hemodynamic effects and long-term clinical benefits of ACE inhibitors was the first indication that mechanisms other than improvement in left ventricular systolic performance may be responsible for their long-term clinical benefits (5).

The research of Pfeffer and colleagues on an experimental model of heart failure provided a clearer understanding of the mechanisms responsible for the clinical benefits of ACE inhibitors in patients with CHF (6, 7). In a landmark publication, these investigators reported that ACE inhibition with captopril reduced LV dilatation in a rat model of myocardial infarction (MI) after occlusion of the left anterior descending (LAD) coronary artery (8). Subsequently, Pfeffer and colleagues extended their experimental observations to patients with recent MI and significantly depressed LV ejection fraction (LVEF) (9, 10). However, in contrast to the reversal of the LV remodeling process in patients with recent MI, ACE inhibitors only attenuated the progression of the LV remodeling process in patients with chronic LV systolic dysfunction (11). Moreover, the modest effect of ACE inhibitors on LV remodeling in patients with CHF cannot explain the substantial improvement in functional status noted after several weeks of therapy. Previous studies have shown that during exercise, an increase in skeletal muscle perfusion is largely responsible for any improvement in functional status (12). Over a period of time, ACE inhibitors exert an anti-remodeling vascular effect, as evidenced by regression of the peripheral vascular abnormalities that accompany the CHF syndrome. The unexpected but repeatedly reported findings that ACE inhibition prevents recurrence of MI or unstable angina strongly suggest a direct vascular effect on the coronary circulation and/or an alteration in the progression of atherosclerosis (13–18). The results of the Heart Outcomes Prevention Evaluation (HOPE) trial provide further evidence supporting the effects of ACE inhibitors on the coronary and peripheral vasculature (19, 20). Patients without LV systolic dysfunction who were at high risk for vascular events were shown to have a lower incidence of vascular events while receiving ramipril. The observed improvement in vascular endothelial function resulting from ACE inhibition may contribute greatly to this effect (21, 22). Thus, the rationale for the use of ACE inhibitors in patients with CHF evolved from the paradigm of afterload reduction to that of LV anti-remodeling effect and later to the present one, of vascular protection. The changing paradigms (Fig. 1) regarding ACE inhibition in CHF will now be reviewed.

ACE Inhibitors as Vasodilator Therapy

The initial rationale behind the clinical trials of administering ACE inhibitors to patients with CHF was to optimize the loading conditions imposed on the failing heart by reducing peripheral vascular resistance, thereby enhanc-

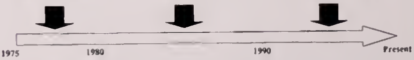
Reduction of Cardiac Preload and Afterload
Attenuation of Left Ventricular Remodeling
Vascular Protection
1975
1980
1990
Present

Fig. 1. Changing paradigms behind the use of angiotensin-converting enzyme (ACE) inhibitors for the treatment of chronic heart failure. From the mid-1970s to the early 1980s, the rationale was to reduce cardiac preload and afterload. In the 1980s, the rationale changed to attenuation of left ventricular remodeling. The current rationale for ACE inhibition in patients with cardiovascular disease is vascular protection.

ing cardiac output. The hemodynamic effectiveness of vasodilator therapy in the treatment of heart failure was first demonstrated with the use of hydralazine and subsequently with hydralazine and isosorbide dinitrate, a combination that reduces both cardiac preload and afterload (1). The impetus toward the use of ACE inhibitors in CHF was to duplicate with one agent the hemodynamic effects produced by hydralazine and isosorbide dinitrate. Captopril, the first oral ACE inhibitor approved by the Food and Drug Administration (FDA), enhanced cardiac output and lowered LV filling pressure while producing modest reductions in systolic blood pressure and heart rate in patients with CHF due to LV systolic dysfunction (2). In contrast to the long-term alpha-adrenergic blockade that is associated with attenuation of hemodynamic effects, long-term ACE inhibition with captopril produces sustained hemodynamic effects.

In view of the beneficial effect on mortality reported with the combination of hydralazine and isosorbide dinitrate for patients with CHF in the Vasodilators in Heart Failure Trial (V-HeFT-I) (23), the effects on mortality of long-term use of ACE inhibition with enalapril were investigated by the CO-operative North Scandinavian ENalapril SUrvival Study (CONSENSUS) trial for patients with severe CHF, defined as New York Heart Association (NYHA) functional class IV (24). Long-term administration of enalapril reduced mortality by 31% when compared to placebo. The beneficial effect of long-term ACE inhibition on mortality was subsequently extended to less symptomatic patients in the Studies Of Left Ventricular Dysfunction (SOLVD) trial (18). Patients enrolled in the treatment arm of the SOLVD trial had symptoms compatible with NYHA functional classes II–III. With a mean follow-up of 41.4 months, enalapril reduced mortality by 16% when compared to placebo, during the first 24 months of follow-up. Thereafter, the number of deaths of patients randomized to enalapril or placebo was similar. Patients with LV systolic dysfunction deemed to be asymptomatic, since they did not require therapy for heart failure, were enrolled in the prevention arm of the SOLVD trial. The mean LVEFs in the treatment and prevention arms were 25% and 28%, respectively. This small difference in LVEF between symptomatic and asymptomatic patients provides further evidence of the dissociation of LV systolic performance and functional capacity, which derives from the fact that symptoms are related to the inadequacy of the peripheral circulation, while depression of LVEF predicts mortality and not symptoms. During a mean follow-up of 37.4 months, enalapril did not significantly affect mortality in asymptomatic patients with CHF (25).

In the second Vasodilator Heart Failure Trial (V-HeFT-II), conducted by the Veterans Administration, Cohn and colleagues compared the effects of enalapril and the hydralazine-isosorbide dinitrate combination on mortality (4). Although the hydralazine-isosorbide dinitrate combination increased LVEF to a greater extent than did enalapril, enalapril had a significantly greater effect on mortality (Fig. 2). Enalapril resulted in a 28% risk reduction in mortality when compared to hydralazine and isosorbide dinitrate. The dissociation between the effect of enalapril on LVEF and mortality also suggests that ACE inhibition reduces mortality by mechanisms other than a change in LV systolic performance.

Left Ventricular Remodeling and ACE Inhibition

Pfeffer and colleagues have extensively studied the rat model of MI induced by LAD artery occlusion (6, 7). When LAD artery occlusion results in a relatively small MI (<30% of the LV circumference), the rats do not have discernible impairment in LV performance. When LAD artery occlusion results in moderate MI (31–46% of the LV circumference), LV systolic performance is normal at rest but reduced during stress, i.e., impaired LV reserve. When LAD artery occlusion results in a large MI (greater than 46% of the LV circumference), rats have evidence of congestive heart failure with reduced cardiac output at rest, despite elevated LV filling pressure. Using this well-char-

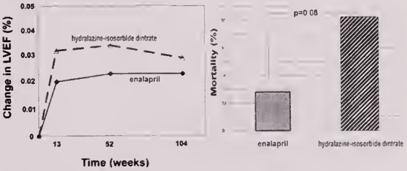

Fig. 2. Effects of hydralazine-isosorbide dinitrate (broken line and hatched bar) and enalapril (solid line and bar) on left ventricular ejection fraction (LVEF, %) and mortality in the V-HeFT II trial (4). Enalapril had a significantly greater effect on mortality, although it increased LVEF to a lesser extent than hydralazine-isosorbide dinitrate.

acterized model of heart failure, Pfeffer and colleagues demonstrated that long-term ACE inhibition with captopril prevents or attenuates the progressive LV dilatation and deterioration of LV systolic performance which occur in rats after complete LAD artery occlusion (8). Of note, the effect of captopril on survival was most apparent in rats with MI of moderate size (9). In rats, survival was not affected by captopril when mortality either was extremely low with a small MI or extremely high with a large MI. The beneficial effect of long-term administration of captopril in this experimental model of heart failure led Pfeffer and colleagues to undertake a double-blind, placebo-controlled, randomized trial for patients with their first MI and LVEF below 45% (10). After administration of the study drug for 12 months, LV end diastolic (LVED) volume had increased by 21 ± 8 mL in patients randomized to placebo, and by 10 ± 6 mL ($p<0.02$) for patients randomized to captopril. The attenuation of the remodeling effect of captopril was most apparent in a subset of patients at high risk due to persistent occlusion of the LAD artery. Thus, similarly to what was observed in rats after LAD artery occlusion, ACE inhibition with captopril prevents or attenuates the LV remodeling process after MI in humans.

The beneficial effects of captopril on LV remodeling provided the rationale for the Survival And Ventricular Enlargement (SAVE) trial (14). Another objective was to study the effects of long-term administration of captopril on the mortality of patients who had suffered a recent MI and had an LVEF below 40%. Among the 2,231 patients randomized, there were 228 deaths (20%) in the captopril group and 275 (25%) in the placebo group. The risk reduction in mortality was 19% (95% CI 3–32%, $p=0.019$). Thereafter, several other large trials confirmed these findings of the SAVE trial.

The work of Pfeffer and others has convincingly demonstrated that long-term ACE inhibition reverses or attenuates the LV remodeling process after a recent MI. The data regarding the effects of long-term ACE inhibition on the LV remodeling process in patients with chronic LV systolic dysfunction are less convincing. The effects of enalapril on LVED volume as determined by radionuclide ventriculography were evaluated by Konstam and colleagues in a subset of patients enrolled in the SOLVD trial (Fig. 3) (25, 26). Within weeks of initiation of enalapril, LVED volume had decreased substantially. Conversely, LVED volume had substantially increased as soon as 2 weeks after withdrawal of enalapril. The time course of the change in LVED volume after initiation and withdrawal of enalapril strongly suggests that alterations in cardiac loading conditions rather than a primary anti-remodeling effect were mostly responsible for the change in LV volume. While a direct vasodilating effect of enalapril was no longer present 2 weeks after its withdrawal, cardiac loading conditions had not returned to baseline, due to persistence of the anti-remodeling effect of enalapril on the peripheral circulation. As this latter effect wore off, LVED volume was likely to have further increased.

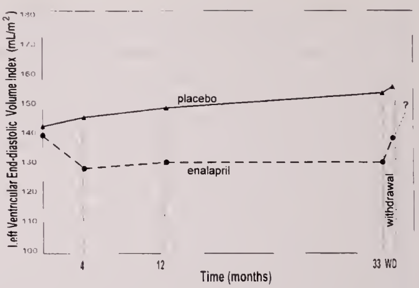

Fig. 3. Effect of enalapril (broken line) and placebo (solid line) on left ventricular end-diastolic (LVED) volume index (mL/m^2) in a subset of patients enrolled in the SOLVD trial (25, 26). The rapid change in LVED volume index within weeks of initiation and withdrawal of enalapril therapy suggests that the concomitant alterations in cardiac loading conditions were primarily responsible for the change in LVED volume index. WD = withdrawal.

The effect of long-term ACE inhibition with enalapril on LVED volume was studied by two-dimensional echocardiography in a subset of patients enrolled in the prevention arm of the SOLVD trial (11). Over 12 months, LVED volume increased from 200 ± 42 mL to 210 ± 46 mL in the placebo group while LVED volume remained unchanged, 196 ± 41 mL to 197 ± 39 mL, in the enalapril group. Thus, long-term administration of enalapril attenuated, but did not reverse, the LV remodeling process. As noted in the previously mentioned radionuclide study of the SOLVD trial, concomitant alterations in cardiac loading conditions are likely to have contributed to the attenuation of the remodeling process.

Lastly, the effects of long-term ACE inhibition with captopril on LV cavity area at end- diastole were evaluated by 2D echocardiography of 512 patients enrolled in the SAVE trial (27). Captopril-induced attenuation of the LV remodeling process was most apparent during the first 12 months of the SAVE trial. Thereafter, LV cavity areas at end-diastole increased at a comparable rate in patients randomized to captopril or placebo. Such an observation is reminiscent of the escape from ACE inhibition phenomenon that was reported during long-term ACE-inhibitor therapy for patients with hypertension (28). Early in the course of ACE inhibition, plasma angiotensin II levels are substantially lower than at baseline, but with time, plasma angiotensin II levels rise steadily above baseline values (29).

In summary, the effects of ACE inhibitors on LVED volumes are modest and are in part mediated by favorable alterations in cardiac loading conditions in patients with chronic LV systolic dysfunction. Moreover, attenuation of the LV remodeling process cannot by itself account for the clinical benefits of long-term ACE inhibition in patients with CHF.

Vascular Protection and ACE Inhibition

While ACE inhibitors were being investigated for the treatment of CHF and MI, two unexpected observations attracted the attention of the investigators to the effects of ACE inhibition on the peripheral and coronary circulation. Although ACE inhibition consistently improved LV systolic performance in patients with CHF, peak aerobic capacity in exercise improved only in patients who experienced an increased dilatory response of the skeletal muscle vasculature to exercise, with an increase in skeletal muscle blood flow. Improvement in peak aerobic capacity is closely related to an increase in skeletal muscle perfusion, and is independent of the improvement in left ventricular performance (12). In contrast to the improvement in LV systolic performance that occurs immediately after the initiation of therapy, the increase in skeletal muscle perfusion and, thereby, functional capacity is delayed in time, measured in weeks. Thus, the increase in skeletal muscle perfusion is presumably due to the vascular anti- remodeling effect of ACE inhibitors, and this only occurs over a period of time.

The importance of vascular events was further demonstrated in several large placebo-controlled trials of ACE inhibitors in patients with CHF and MI (Fig. 4) (13). Thus, in patients receiving ACE inhibitors, an unexpectedly lower incidence of recurrent MI was noted as compared to placebo. The risk reduction in the likelihood of recurrent MI ranged from 11–25%. In contrast to the effect of the ACE inhibitors on mortality that is observed immediately after initiation of therapy, the effect on prevention of recurrent MI was delayed for at least 4 months after initiation of therapy. How long-term ACE inhibition serves to prevent recurrence of MI is still incompletely understood. The well-documented anti-atherogenic, anti-inflammatory, antiproliferative and antithrombotic properties of ACE inhibitors in experimental preparations are likely to contribute to the prevention of MI in patients with coronary artery disease (CAD) (30). Lastly, the delayed effect of ACE inhibitors in prevention of recurrent MI is analogous to the previously mentioned delay in improvement of skeletal muscle perfusion and peak aerobic capacity in patients with CHF. These two unexpected observations provided the rationale to test the hypothesis that the vascular effects of ACE inhibitors may result in vascular protection in patients with vascular conditions such as stroke, transient ischemic attack, hypertension, peripheral artery disease or diabetes, even in the absence of LV dysfunction.

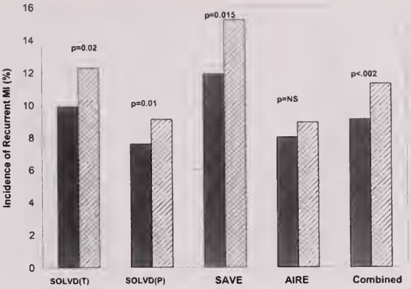

Fig. 4. Incidence of recurrent myocardial infarction (MI, %) in patients receiving an angiotensin-converting enzyme (ACE) inhibitor (solid bars) and in patients receiving placebo (hatched bars) reported in the Treatment (T) and Prevention (P) arms of SOLVD, and the SAVE and AIRE trials (references 13–15, 18, 23). The combined risk reduction provided by ACE inhibition averages 21%.

This "vascular" hypothesis was tested in the HOPE trial (Fig. 5) (19, 20). In this trial, 9,297 high-risk vascular patients who presumably had normal LV systolic performance were randomized to ramipril or placebo. The mean duration of follow-up was 4.5 years. MI, stroke and death from cardiovascular causes occurred in 651 and 826 patients receiving ramipril and placebo, respectively. The relative risk reduction was 22% (relative risk 0.78, 95% CI 0.70–0.86, $p<0.001$). The beneficial effects of

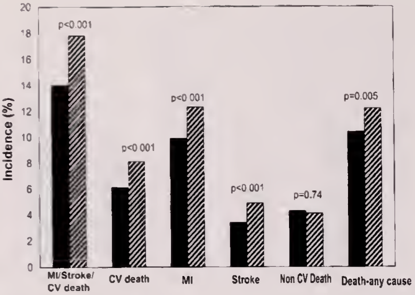

Fig. 5. Incidence of myocardial infarction (MI) / stroke / cardiovascular (CV) death, CV death, MI and stroke alone, non-CV death and death, from any cause, of patients receiving ramipril (solid bars) and patients receiving placebo (hatched bars) as reported by the investigators of the HOPE trial (19).

ramipril on outcome in this high-risk vascular population cannot be ascribed to an attenuation of the LV remodeling process. Rather, these beneficial effects probably result from multiple effects on the vasculature, which include attenuation of the direct vasoconstrictor effects of angiotensin II, attenuation of proliferation of vascular smooth muscle cells and fibrinolysis, as well as improvement of vascular endothelial function (31).

The investigators of the Trial on Reversing ENdothelial Dysfunction (TREND) were the first to demonstrate that sustained ACE inhibition improves vascular endothelial function (32). One hundred and twenty-nine patients with CAD were randomized for 6 months to quinapril or placebo. Coronary artery diameter response to incremental concentrations of acetylcholine was assessed by quantitative angiography. Response to acetylcholine was improved in patients receiving quinapril when compared to the response of patients receiving placebo: 4.5 ± 3.0% versus –0.1 ± 2.8% at 10^{-6} mol/L and 12.1 ± 3.0% versus –0.8 ± 2.9% at 10^{-4} mol/L, respectively (overall p=0.002). Several mechanisms may mediate the effect of quinapril on vascular endothelial function. They include enhanced vascular smooth muscle relaxation resulting from lower local concentrations of angiotensin II and greater nitric oxide availability resulting from decreased generation of superoxide as well as increased nitric oxide production by elevated levels of kinins.

In addition to improving vascular endothelial function, ACE inhibitors delay progression of human vascular atherosclerosis. In the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE), 693 patients were randomized 1:1 to ramipril or placebo (33). Mean maximum carotid intimal medial thickness (IMT) was serially measured during an average follow-up of 4.5 years. The rate of progression of the mean maximum carotid IMT was 0.0217 mm/yr in the placebo group and 0.0137 mm/yr in the ramipril 10 mg/day group (p=0.033). The anti-atherogenic action of ramipril is probably due to reduced local angiotensin II concentration and to bradykinin potentiation, both resulting in decreased proliferation and migration of smooth muscle cells, and decreased activation of inflammatory cells.

The results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), involving patients with a history of stroke or transient ischemic attack (TIA), also point to the clinical relevance of the above-mentioned anti-atherogenic effects of ACE inhibitors (34). When compared to patients receiving placebo, those receiving perindopril experienced a risk reduction of 28% in stroke and 26% in vascular events (stroke / MI / cardiovascular death).

Summary

The evolving rationale behind the use of ACE inhibitors has led to considerable broadening of their indications for patients with cardiovascular disease. First approved for the treatment of hypertension, ACE inhibitor therapy was subsequently recognized as the first pharmacological intervention that positively impacts on survival of patients with CHF. Thereafter, the indication for ACE inhibitor therapy was extended to patients with recent MI. The progressive understanding that the vascular effects of ACE inhibitors are responsible for most of their clinical benefits led to the paradigm of vascular protection and their approval for high-risk vascular patients. Several issues remain to be answered regarding the use of ACE inhibitors for vascular protection. One such issue is whether ACE inhibition can result in long-term vascular protection in asymptomatic patients who are at risk for vascular disease. Molecular genetics may identify patients with high tissue renin-angiotensin system activity, and help select those asymptomatic patients most likely to benefit from long-term ACE inhibition at low doses.

References

1. Kovick RB, Tillisch JH, Berens SC, et al. Vasodilator therapy for chronic left ventricular failure. Circulation 1976; 53:322–328.
2. Chatterjee K, Parmley WW, Cohn JN, et al. A cooperative multicenter study of captopril in congestive heart failure: hemodynamic effects and long-term response. Am Heart J 1985; 110(2):439–447.
3. Davis R, Ribner HS, Keung E, et al. Treatment of chronic congestive heart failure with captopril, an oral inhibitor of angiotensin-converting enzyme. N Engl J Med 1979; 301:117–121.
4. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991; 325(5):303–310.
5. Massie BM, Kramer BL, Topic N. Lack of relationship between the short-term hemodynamic effects of captopril and subsequent clinical responses. Circulation 1984; 69(6):1135–1141.
6. Pfeffer MA, Pfeffer JM, Fishbein MC, et al. Myocardial infarct size and ventricular function in rats. Circ Res 1979; 44:503–512.
7. Fletcher PJ, Pfeffer JM, Pfeffer MA, Braunwald E. Left ventricular diastolic pressure-volume relations in rats with healed myocardial infarction. Effects on systolic function. Circ Res 1981; 49(3):618–626.
8. Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. Circ Res 1985; 57(1):84–95.
9. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. Circulation 1985; 72(2):406–412.
10. Pfeffer MA, Lamas GA, Vaughan DE, et al. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med 1988; 319(2):80–86.
11. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiography substudy. Circulation 1995; 91(10):2573–2581.
12. Mancini DM, Davis L, Wexler JP, et al. Dependence of enhanced maximal exercise performance on increased peak skeletal muscle perfusion during long-term captopril therapy in heart failure. J Am Coll Cardiol 1987; 10:845–850.
13. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet 1992; 340(8829):1173–1178.
14. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. The SAVE investigators. N Engl J Med 1992; 327:669–677.
15. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342:821–828.
16. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med 1995; 332:80–85.
17. Torp-Pedersen C, Kober L for the TRACE Study Group. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. Lancet 1999; 354:9–12.
18. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991; 325(5):293–302.
19. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342:145–153.
20. Dagenais GR, Yusuf S, Bourassa MG, et al. Effects of ramipril on coronary events in high- risk persons: results of the Heart Outcomes Prevention Evaluation Study. Circulation 2001; 104:522–526.
21. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation. 2000; 101(16):1899–1906.
22. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation. 2000; 101(9):948–954.
23. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 1986; 314:1547–1552.
24. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987; 316:1429–1435.
25. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992; 327:685–691.
26. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation 1992; 86:431–438.
27. St John Sutton M, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long- term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. Circulation 1997; 96:3294–3299.
28. Ennezat PV, Berlowitz M, Sonnenblick EH, Le Jemtel TH. Therapeutic implications of escape from angiotensin-converting enzyme inhibition in patients with chronic heart failure. Curr Cardiol Rep 2000; 2(3):258–262.
29. MacFadyen RJ, Lee AF, Morton JJ, et al. How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? Heart 1999; 82(1):57–61.
30. O'Keefe JH, Wetzel M, Moe RR, et al. Should an angiotensin-converting enzyme inhibitor be standard therapy for patients with atherosclerotic disease? J Am Coll Cardiol 2001; 37(1):1–8.
31. Higashi Y, Sasaki S, Nakagawa K, et al. A comparison of angiotensin-converting enzyme inhibitors, calcium antagonists, beta-blockers and diuretic agents on reactive hyperemia in patients with essential hypertension: a multicenter study. J Am Coll Cardiol 2000; 35(2):284–291.
32. Mancini GB, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. Circulation 1996; 94(3):258–265.
33. Lonn E, Yusuf S, Dzavik V, et al. Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). Circulation 2001; 103(7):919–925.
34. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure- lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358(9287):1033–1041.

Glycoxidation:

The Menace of Diabetes and Aging

Helen Vlassara, M.D.[1], and Marcia Rashelle Palace, M.D.[2]

Abstract

Advanced glycation end products (AGE) form via the Maillard reaction *in vivo* and are also consumed from exogenous sources such as diet and smoking. They alter the structure and function of molecules and increase oxidative stress in biological systems. These consequences promote the pathogenesis of diabetic complications and changes associated with aging, including atherosclerosis, and renal, eye, and neurological disease. Both specific and nonspecific receptor mechanisms mediate these detrimental effects but also participate in the removal and degradation of AGE. AGE toxicity may be averted by promising dietary and pharmacological strategies which are currently being investigated.

Key Words: Glycoxidation, advanced glycation end product, oxidative stress, macroangiopathy, microangiopathy.

Introduction

Acute metabolic derangements associated with hyperglycemia are well recognized. However, only relatively recently have we become truly aware of the irreversible diabetic changes caused by elevated glucose. It is now accepted that sustained hyperglycemia causes permanent changes which promote development of progressive dysfunction, leading to diabetic complications (1). One such detrimental consequence of hyperglycemia is the formation of advanced glycation end products (AGEs) *in vivo*, via the Maillard reaction. As bioreactive molecules, AGEs have a range of chemical, cellular, and tissue effects through which they mediate not only diabetic complications, but also widespread changes associated with aging. Furthermore, the main exogenous sources of AGEs, including cigarette smoking and consumption of foods processed by heating, similarly pose major detrimental effects to living organisms.

The following review focuses on the role that advanced glycation plays in the initiation and progression of diabetic complications, the mechanisms by which AGEs exert their effects, and the *in vivo* systems that are involved in their degradation and removal. We also discuss strategies, both dietary and pharmacological, that can lessen the physiological burden of AGEs and curtail the widespread damage they impose on biological systems.

Exogenous AGE Sources

While the *in vivo* formation of AGEs detailed below clearly mediates multiple pathological processes, it is becoming apparent that exogenous sources of AGEs, such as diet and smoking, may have significant impact on disease mechanisms as well. Diet is the major source of exogenous AGE, with the highest content in cooked foods, particularly those rich in carbohydrates, proteins, and fats. As formation of AGE is enhanced by exposure to heat, AGE content, which is responsible for the browning of food as it cooks, increases with cooking temperature and duration. The existence of AGE compounds found *in vivo,* including methylglyoxal (MG) and carboxymethyl lysine (CML), in the diet has long been recognized by food chemists. However, their pathogenic significance was not appreciated.

---

[1] Professor, Department of Geriatrics, Division of Experimental Diabetes and Aging, and [2] Clinical Fellow, Department of Medicine, Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Helen Vlassara, M.D., Director, Division of Experimental Diabetes and Aging, Box 1640, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; Email: helen.vlassara@mssm.edu

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on November 6, 2001 and updated as of January 2003.

The study of the dietary content, bioavailability, and renal elimination of AGEs, schematically depicted in Fig. 1, has been facilitated by the availability of new AGE-specific assays. It has been confirmed that AGE absorption is approximately 10% of all AGEs ingested (2). Furthermore, only one-third of that absorbed is excreted within 48 hours in the urine of patients with normal renal function (3). AGEs that are not cleared are deposited in tissues where they remain biologically active (3), posing a serious threat to the organism, one that is clearly exaggerated in patients with renal impairment.

In vivo injury as a result of AGE accumulation is exemplified by the fact that when diabetic mice were randomized to receive either a regular diet or one which was otherwise nutritionally identical but had less AGE content, mice on the regular diet developed changes typical of diabetic nephropathy, while mice on the low AGE diet did not, even in the face of persistent hyperglycemia (Fig. 2) (4). Similarly, a low-AGE diet prevented vascular restenosis and atherosclerosis in diabetic, hyperlipidemic, ApoE-deficient mice (see below) (5).

In addition to diet, smoking remains a significant source of exogenous AGE. Glycated and oxidized derivatives form via the Maillard reaction cascade as tobacco leaves are dried in the presence of sugars during the process of curing. Upon combustion, reactive AGE species are volatilized, inhaled and absorbed through the lungs, and become conjugated with serum proteins, including lipoproteins (6). Thus, total serum AGE and AGE-apoprotein B levels (6), as well as arterial (7, 8) and ocular lens AGE levels (8), are significantly higher in smokers than in nonsmokers, and are especially high in diabetic smokers.

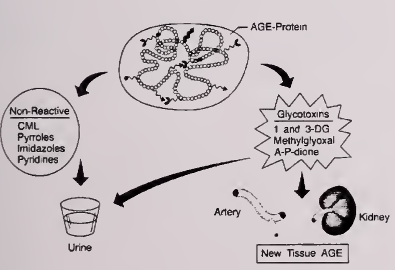

Fig. 1. Schematic representation of the fate of diet-derived AGEs. Protein or lipid glycation intermediates contained in the diet include noncrosslinking products, such as *N-ε-* carboxymethyllysine (CML), pyrroles, imidazoles, pyridines (left insert), and crosslink forming, reactive intermediates (glycotoxins), such as 1-,3-deoxyglycozone (3-DG), methylglyoxal, protein-linked A-P-dione (right insert). While the former are excreted in the urine, the latter may reattach onto serum or tissue components to form pathologic new AGEs.

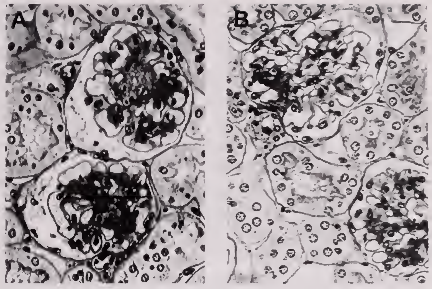

Fig. 2. Development of nephropathic glomerular changes is delayed in diabetic NOD and db/db mice fed a low-AGE diet. **Panel A:** Glomerular changes characteristic of nephropathy in db/db mice after 5 months on standard chow diet (H&E); **Panel B:** Relative sparing of glomeruli in mice fed a diet containing 5-fold lower AGE for 5 months (H&E; magnification × 400).

Endogenous AGE Formation

Over time, even modest hyperglycemia can result in significant accumulation of AGEs on long-lived macromolecules (9–11). This is apparent on certain long-lived proteins such as those of the ocular lens. Lens crystallins are subjected to progressive modification by AGEs, which promotes lenticular browning and cumulative crosslinking (12, 13). The resultant opacification forms cataracts, a process associated with both diabetes and aging (14, 15). These changes, which can be reproduced *ex vivo* under high-glucose conditions, can be prevented by the AGE-inhibitor aminoguanidine (16). Furthermore, the collagen network of human vitreous gel contains increased levels of AGEs in diabetics (16), and vitreous AGE levels show a significant correlation with age, supporting the role of AGEs in diabetes- and age-related vitreous alterations, including progression of retinopathy and posterior vitreal detachments (16).

While glycation of long-lived molecules such as structural proteins was recognized first, it is now apparent that AGEs also arise on short-lived molecules, including circulating plasma proteins and lipids, cytoplasmic proteins and nucleic acids (17). Furthermore, intracellular AGEs may form at a rate of up to 14 times faster in high (30 mM) glucose conditions (18) and are thus found at significantly elevated levels in diabetic patients. Such AGE modification of short-lived molecules is known to be associated with oxidation of proteins and lipids, disrupt molecular conformation, alter enzymatic activity, reduce degradative capacity, and result in abnormal recognition and clearance by receptors (19–22).

Glucose reacts with amino groups on certain phospholipids such as phosphatidylethanolamine to form AGEs (23). Glycation of lipids and lipoproteins occurs, as in the case of apoprotein B (ApoB) and low-density lipoprotein (LDL) (24). The predominant site of such modification of LDL is distal to the N-terminus of the LDL-receptor binding domain (24). Formation of AGE-LDL occurs in direct proportion to glucose concentration. In fact, AGE-ApoB levels are approximately 4-fold higher in diabetic patients than in nondiabetic patients (23, 25).

In vitro LDL oxidation occurs concomitantly with advanced glycation of the lipid component of LDL (24). During glycation, fatty acid residues can be oxidized independently of transition metals or exogenous free-radical generating systems (23). Formation of AGE-LDL and LDL oxidation are both inhibited in the presence of the AGE inhibitor aminoguanidine (23). *In vivo* clearance of injected AGE-LDL was delayed compared to that of native LDL (25) in studies of transgenic mice expressing the human LDL receptor. These data support the role of glycated Apo-B in promoting atherosclerosis, a process that will be described further, below.

AGEs as Mediators of Diabetic Complications

Macroangiopathy

Accumulation of lipids and lipoproteins in the vessel wall, resulting in fatty streaks, is a pivotal factor in the evolution of advanced atherosclerotic lesions, a process of particular concern for diabetics, who have an increased risk for vascular occlusive events (26–28). It is thought that oxidative modification of LDL (ox-LDL) *in vivo* reduces its recognition by the normal LDL receptor (29, 30), thereby decreasing its clearance, increasing serum LDL levels (31, 32), and ultimately promoting enhanced uptake of ox-LDL by scavenger receptors on macrophages and vascular smooth muscle cells.

AGEs, which have been detected within atherosclerotic lesions in both extra- and intracellular locations (33–37), are now considered to play an important role in the initiation and acceleration of atherosclerosis even in normoglycemic patients (33), but especially in diabetics (38, 39) and more so in diabetics with renal insufficiency (34). AGE-ApoB and AGE levels in the vessel wall of carotid arteries from nondiabetic patients have been found to correlate with occlusive disease requiring endarterectomy (33). Furthermore, exposure of endothelial cells to AGEs may enhance procoagulant activity (40) and promote cell adhesion and transendothelial migration (41, 42).

As vascular endothelium expresses receptors for AGEs (43–46), accumulation of AGEs in the subendothelial space may occur as a direct result of endocytosis and transcytosis of AGE- LDL by these receptors. Intracellular accumulation of AGEs may promote phenotypic conversion of smooth muscle cells and foam cell formation within atherosclerotic plaques. This is consistent with the diffuse pattern of AGE deposition and endocytosis by endothelium, smooth muscle cells, and macrophages (34–39, 47). AGE adducts in the vessel wall can interfere with endothelium-derived nitric oxide (NO) synthase and the vasodilatory action of (NO·) (48, 49), as shown in nondiabetic animals which exhibited diabetic-like disruption of vaso-relaxation after AGE-infusion (50). Hypertension, renal impairment, and erectile dysfunction seen in diabetes may be related to these alterations.

Microangiopathy

Diabetic microangiopathy is characterized by the progressive damage of endothelium and associated mural cells in microvascular beds, resulting in capillary occlusion, ischemia, and organ failure. These changes occur in the kidney, retina, and microvasculature of peripheral nerves (51, 52).

Immunohistochemical studies of kidney from normal and diabetic rats have suggested that glomerular basement membrane (BM), mesangium, podocytes, and renal tubular cells accumulate high levels of AGEs. Ultrastructural studies have indicated that AGE peptides may be reabsorbed by the renal proximal tubular cells (53). AGE deposition can lead to glomerulosclerosis and widespread dysfunction independent of diabetes (54–56). This is evidenced by the development, in nondiabetic animals infused with AGE-albumin, of glomerular pathology resembling diabetic nephropathy, including glomerular hypertrophy, BM thickening, mesangial extracellular matrix (ECM) expansion, and albuminuria (50, 57).

In diabetic retinopathy, intraretinal blood vessels become dysfunctional in response to hyperglycemia, with progressive loss of retinal pericytes and eventually of endothelial cells, leading to capillary closure and widespread retinal ischemia. As in other vascular beds, AGEs have been localized in the retinal vessels of diabetics (58, 59). However, their exact role is not defined. Experimental studies have demonstrated that AGEs may be responsible for some retinal pathology (59) and that AGE-inhibitors, such as anti-glycated albumin (60) or aminoguanidine, can prevent the development of diabetes-associated retinal vascular lesions in rats (61) and in dogs (62).

Embryopathy

Like amino acids and lipids, nucleic acids react with reducing intracellular sugars to form Amadori and AGE-products (17). AGE formation on DNA can promote teratogenesis by causing single strand breaks in genomic DNA (17, 63, 64). Teratogenic effects may also be induced in diabetes by enhanced glycation of histone proteins, which normally function to maintain nucleosomes and thus, DNA integrity. Intracellular sugars such as glucose-6-phosphate and adenosine diphosphate (ADP)-ribose react strongly with amino groups on histones, causing crosslinking *in vitro* (65, 66) as well as *in vivo* (67).

It is well recognized that maternal diabetes is associated with congenital malformations and increased fetal mortality and morbidity (68). The incidence of perinatal infant fatalities due to congenital malformations in the offspring of women with insulin-dependent diabetes is increased 2–3-fold compared with those born to nondiabetic mothers (69). The incidence of congenital abnormalities is also increased when conception occurs in the setting of long-term hyperglycemia; this is not the case with short-term, pregnancy-induced hyperglycemia (70). This observation, as well as the marked reduction in fetal abnormalities associated with effective glucose control during pregnancy, supports the role of AGE-mediated teratogenicity in diabetic embryopathy.

AGE-Receptor Systems and Their Regulation

Over the past 15 years, some of the receptor systems mediating AGE-related biology have been elucidated. Several AGE-binding molecules have been described, including a specific AGE-receptor complex composed of R1, R2, and R3 (43, 44, 57, 71–75), receptor for AGE (RAGE) (45, 46), and scavenger receptors such as CD-36 (76) and SCR-II (77, 78).

Evidence indicates that AGE-R1 and -R3, components of the AGE-receptor complex, are largely responsible for AGE-recognition and high-affinity binding (43, 75). AGE-R2 is subject to AGE-induced phosphorylation (44). This suggests it plays a role in signal transduction and cell activation associated with AGE-receptor binding (41, 79).

RAGE, a multiligand member of the immunoglobulin superfamily, though less efficient in AGE endocytosis and turnover (80), is viewed increasingly as an intracellular signal- transducing or pro-inflammatory peptide. In this regard, RAGE may thus be more accurately classified in the family of oxidant-stress-inducing signaling molecules or co-factors. Consistent with the above, in animal models, brief infusion of soluble, truncated RAGE is reported to intercept diverse processes such as endothelial leakage, atherosclerosis, and inflammatory bowel disease (45, 80).

Specific and saturable binding of AGE-BSA (bovine serum albumin) to CD36-CHO (Chinese hamster ovary) cells supports the role of CD-36 as a receptor for AGE-proteins (76). As with RAGE, this scavenger receptor system, which is highly expressed on macrophages, may contribute to AGE-mediated cellular changes, particularly in the context of atherosclerosis and foam cell formation (77, 81, 82).

AGE-receptor systems may be regulated by diabetic factors such as glucose, insulin, AGEs, and reactive oxygen species (ROS) (58, 83–85). Most commonly used measures for assessing AGE-receptor modulation have centered on parameters of cell activation. While the link between AGE-receptor upregulation and cellular activation has been confirmed for a number of the presently identified receptor components, cell activation can also occur by nonreceptor pathways, or by intracellularly generated glycoxidant derivatives, leading to ROS generation and oxidant stress (72, 86).

The macrophage AGE-receptor system, which is the one most closely linked to AGE-turnover, was initially thought to include autoregulatory switches, allowing it to respond to rising AGE levels and to reduce tissue damage (83, 84). However, the means by which this balance is maintained *in vivo* during times of excessive AGE accumulation remains largely unknown. Possibly, metabolic or genetic factors could tip this balance toward pro-inflammatory events via receptor components tied to signaling (e.g., RAGE, AGE-R2, or AGE-R3) or by receptor-independent mechanisms (43, 45, 72, 73, 81). Alternatively, it could be that delayed AGE processing and disposal, due to lack or malfunction of the endocytotic portion of the AGE-receptor, promotes cytotoxic inflammatory events, leading to organ damage, as shown experimentally in AGE-R3 deficient mice (87, 88). Findings of suppressed AGE-receptor uptake and degradation, combined with high circulating and kidney AGE levels in nonobese diabetic (NOD) mice support this hypothesis (89, 90).

Consistent with the animal data, reduced expression of AGE-R1 in human peripheral blood mononuclear cells (PBM) and in immortalized lymphoblasts from type one diabetic (T1D) patients with severe diabetic nephropathy was associated with elevated serum AGE levels and severe diabetic complications (91, 92). These data indicate that genetic modulation of the receptor system may contribute to organ damage in complication-prone patients, while other patients are spared.

For a number of the AGE-receptor-related molecules, the genomic organization and chromosomal location (45, 93 – 95), as well as several prevalent gene polymorphisms (96, 97), have come to light. Recently, screening for mutations was performed in 48 insulin-dependent diabetes mellitus (IDDM) patients with or without nephropathy, using single-stranded conformational polymorphism (SSCP) analysis and direct sequencing of allelic polymerase chain reaction (PCR) fragments (96). Thus far, none of the polymorphisms found have exhibited a clear connection to diabetic complications.

Elimination of AGE-Crosslinks

In vivo removal of AGE crosslink is accomplished largely through extracellular proteolysis and by scavenger cells such as tissue macrophages which ingest AGEs via AGE- specific or nonspecific receptors. Furthermore, mesenchymal cells such as vascular endothelium and mesangium seem to function in AGE elimination, as suggested by the increased endocytic activity of vascular endothelium under conditions of high glucose *in vivo* and *in vitro* (98, 99).

After endocytosis, AGE macromolecules undergo intracellular degradation and are subsequently released as low-molecular-weight AGEs, known as "second-generation AGEs" (100), which include newly exposed reactive intermediates (101 – 105). Renal clearance subsequently limits the toxicity of these compounds. Kidney dysfunction results in failure to clear circulating AGEs, accounting in large part for the marked elevation of serum and tissue AGE levels observed in patients with renal insufficiency (101 – 105) and probably contributing to the acceleration of extrarenal vascular damage in patients with end-stage renal disease (ESRD).

Intracellular protective systems also limit the accumulation of reactive AGE intermediates. For example, the degradative glyoxalase enzymes metabolize the reactive dicarbonyl methylglyoxal to *S*-D-lactoylglutathione, employing reduced glutathione as a cofactor. The significance of such systems is underscored by studies in which glyoxalase-1 expression was upregulated by gene transfection in endothelial cells, resulting in significant inhibition of AGE-mediated cell abnormalities such as increased endocytosis (106). However, these systems can be attenuated under conditions of excess AGE burden, such as in diabetes, hyperlipidemia, or renal failure, or in organisms consuming an AGE-rich diet.

Recently, lysozyme (LZ), the ubiquitous host-defense protein, has been shown to exhibit high-affinity AGE-binding (Kd=50 nM) (107, 108). Interestingly, lysozyme contains a 17-amino-acid-long AGE-binding cysteine-bounded domain termed ABCD loop (107). *In vitro*, LZ suppressed the AGE-enhanced expression of several important modulators of kidney structure and function such as platelet-derived growth factor (PDGF)-B, $\alpha 1$ type IV collagen, and tenascin mRNA in cultured mesangial cells. LZ also normalized the AGE-suppressed MMP-9 gene expression and activity (109). *In vivo* LZ administration to NOD and *db/db* (+/+) mice normalized serum levels of AGE, increased urinary AGE clearance, and improved albuminuria in both diabetic animal models (110, 111). These data have promising implications for the development of preventive interventions to thwart AGE-associated disease processes.

Anti-AGE Strategies

As an understanding of the biology of AGEs has evolved, strategies to forestall their adverse effects have developed. Several approaches which seek to decrease accumulation of exogenous AGE, prevent AGE-formation, reduce AGE effects on cells, and break pre-existing AGE crosslink have been studied.

As diet provides a significant source of exogenous AGE, recent work has focused on determining whether it represents a modifiable risk factor for the development of AGE-induced pathology. One *in vivo* study maintained ApoE-deficient mice on chow which was either high or low in AGE content, for a total of five weeks. After one week, a femoral artery denudation injury was induced and the designated diet was maintained for another four weeks before the injured arteries were examined. Injured arteries in the animals fed the low-AGE diet showed a significant reduction in neointimal area (Fig. 3), and these animals developed less complex lesions with fewer foam cells within the neointima, associated with a 40% decrease in serum AGE levels (112).

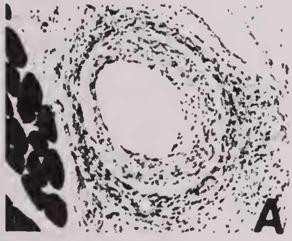

Fig. 3. Post-injury arterial restenosis is delayed in ApoE-deficient diabetic mice fed low-AGE diet. Cross-sections of injured arteries four weeks after transluminal endothelial denudation. The injury was inflicted one week after the mouse began a specific diet, which was continued until the time of sacrifice. **Panel A** represents the injured region of a mouse on the low-AGE diet while **Panel B** represents that of a mouse on the high-AGE diet. (CME staining; magnification × 200).

Similarly, Apo-E-deficient streptozocin-diabetic mice which were fed a diet with AGE content tenfold lower than that of regular rodent chow had significantly suppressed aortic atherogenesis compared to animals on the regular chow, despite the persistence of elevated lipid levels. This was associated with a significant reduction in serum AGE levels (5).

A recent study of human subjects compared the effects of two diets which differed by 6-fold in their AGE content but were otherwise nutritionally equivalent. Eleven diabetic subjects with normal renal function were enrolled in the crossover study; they followed each diet for a two-week period separated by a two-week washout. After two weeks on the low-AGE diet, there was a significant decrease in fasting serum AGE levels. Furthermore, blood mononuclear cell expression of tumor necrosis factor (TNF)-alpha mRNA and serum levels of vascular cell adhesion molecule-1 (VCAM-1), which were significantly higher at the end of the high-AGE diet period, decreased by approximately 30–50% at the end of the low-AGE diet period (113). This reduction in levels of inflammatory mediators in humans, along with the animal data above (5, 112), underscores the potential role of a low-AGE diet in the primary prevention of atherosclerosis as well as in the prevention of restenosis after coronary angioplasty.

Other strategies in the prevention of AGE-related disease have concentrated on pharmacological interventions. The terminal amino group of the small nucleophilic hydrazine compound aminoguanidine, by virtue of its low pKa, reacts specifically with glucose-derived reactive intermediates to prevent crosslinking (114). Aminoguanidine has been shown to prevent diabetes-related vascular complications in experimental animals (23, 61, 62, 115–122). In humans, a phase I clinical trial of aminoguanidine measured advanced glycation-modified hemoglobin (AGE-Hb) in treated and untreated diabetic subjects and found that AGE-Hb, as well as LDL, was significantly reduced in the treated group (25). The fact that glycosylated hemoglobin values were not affected by aminoguanidine treatment underscores the specificity of aminoguanidine for inhibition of post-Amadori, advanced-glycation reactions. Other AGE-inhibiting drugs have been under development, including the thiazolidine derivative OPB-9195, which has been shown to prevent the progression of diabetic glomerulosclerosis in rats (123). One strategy for negating adverse AGE effects has been the employment of neutralizing antibodies against glycated albumin. This has been shown to prevent BM thickening in diabetic db/db mice without affecting the glycemic status of the animals (60). Another approach has employed lysozyme linked to a sepharose matrix facilitating the selective depletion of AGEs from sera or dialysate in diabetic patients with kidney disease (124).

A recent therapeutic aim has been to "break" the irreversible intermolecular crosslinks in tissue and render them renally excretable (125, 126). N-phenyl-thiazolium bromide (PTB) attacks covalent carbon-carbon bonds of dicarbonyl-derived crosslinks *in vitro* (125). The AGE-breaker ALT-711 reverses AGE-mediated vascular stiffness and distensibility in diabetic rats (127). It is hoped that these and other innovations in AGE biology will empower humanity to forestall the ubiquitous disease processes associated with diabetes and with aging.

References

1. Engerman RL, Kern TS. Progression of incipient diabetic retinopathy during good glycemic control. Diabetes 1987; 36:808–812.
2. Sgarbieri VC, Amaya J, Tanaka M, Chichester CO. Nutritional consequences of the Maillard reaction. Amino acid availability from fructose-leucine and fructose-tryptophan in the rat. J Nutr 1973; 103:657–663.
3. Kochinsky T, He CJ, Mitsuhashi T, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci U S A 1997; 94:6474–6479.
4. Zheng F, He C, Li J, Vlassara H. Restriction of AGE content of food without lowering protein intake prevents diabetic nephropathy in mice [abstract]. Diabetes Suppl 2000; 49:A161 (#662-P).
5. Lin R-Y, Choudhury R, Fisher E, et al. Suppression of atherosclerotic lesions by dietary restriction of advanced glycation end products in diabetic Apo-E deficient C57BL/6J mice [abstract]. Diabetes 2001; 50(Suppl):A8.
6. Cerami C, Founds H, Nicholl I, et al. Tobacco smoke is a source of toxic reactive glycation products. Proc Natl Acad Sci U S A 1997; 94:13915–13920.
7. Founds H, Giordano D, Stitt AW, et al. Tobacco smoke is a source of advanced glycation end products (AGEs): possible role in the accelerated vascular disease of smokers [abstract]. J Investig Med 1996; 44:A200.
8. Nicholl ID, Stitt AW, Moore JE, et al. Increased levels of advanced glycation endproducts in the lenses and blood vessels of cigarette smokers. Mol Med 1998; 4(9):594–601.
9. Sell DR, Monnier VM. End-stage renal disease and diabetes catalyze the formation of a pentose derived crosslink from aging human collagen. J Clin Invest 1990; 85:380–384.
10. Monnier VM, Cerami A. Nonenzymatic browning in vivo: possible process for aging of long-lived proteins. Science 1981; 211:491–493.
11. Kohn RR, Cerami A, Monnier VM. Collagen aging in vitro by nonenzymatic glycosylation and browning. Diabetes 1984; 33:57–59.
12. Harding JJ, Crabbe MJC. The lens: development proteins, metabolism and cataract. In: Davson H, editor. The eye. Vol. 1b. New York: Academic; 1984. pp. 207–492.
13. Stevens VJ, Rouzer CA, Monnier VM, Cerami A. Diabetic cataract formation: potential role of glycosylation of lens crystallins. Proc Natl Acad Sci U S A 1978; 75:2918–2922.
14. Monnier VM, Stevens VJ, Cerami A. Maillard reactions involving proteins and carbohydrates in vivo: relevance to diabetes mellitus and aging. Prog Food Nutr Sci 1981; 5:315–327.
15. Matsumoto K, Ikeda K, Horiuchi S, et al. Immunochemical evidence for increased formation of advanced glycation end products and inhibition by aminoguanidine in diabetic rat lenses. Biochem Biophys Res Commun 1997; 241:352–354.
16. Stitt AW, Moore J, Sharkey JA, et al. Advanced glycation end products in vitreous: structural and functional implications for diabetic vitreopathy. Invest Ophthalmol Vis Sci 1998; 39:2517–2523.
17. Bucala R, Model P, Cerami A. Modification of DNA by reducing sugars: a possible mechanism for nucleic acid aging and age-related dysfunction in gene expression. Proc Natl Acad Sci U S A 1984; 81:105–109.
18. Giardino I, Edelstein D, Brownlee M. Nonenzymatic glycosylation in vitro and in bovine endothelial cells alters basic fibroblast growth factor activity. A model for intracellular glycosylation in diabetes. J Clin Invest 1994; 94:110–117.
19. Brownlee M, Vlassara H, Cerami A. Inhibition of heparin-catalyzed human antithrombin III activity by nonenzymatic glycosylation. Possible role in fibrin deposition in diabetes. Diabetes 1984; 33:532–535.
20. Watkins NG, Thorpe SR, Baynes JW. Glycation of amino groups in protein. Studies on the specificity of modification of RNAase by glucose. J Biol Chem 1985; 260:10629–10636.
21. Vitek MP, Bhattacharya K, Glendering JM, et al. Advanced glycation end products contribute to amyloidosis in Alzheimer disease. Proc Natl Acad Sci U S A 1994; 91:4766–4770.
22. Tsilibary EC, Charonis AS, Reger LA, et al. The effect of nonenzymatic glucosylation on the binding of the main noncollagenous NC1 domain to type IV collagen. J Biol Chem 1988; 263:4302–4308.
23. Bucala R, Makita Z, Koschinsky T, et al. Lipid advanced glycosylation: pathway for lipid oxidation in vivo. Proc Natl Acad Sci U S A 1993; 90:6434–6438.
24. Bucala R, Mitchell R, Arnold K, et al. Identification of the major site of apolipoprotein B modification by advanced glycosylation end products blocking uptake by the low density lipoprotein receptor. J Biol Chem 1995; 270:10828–10832.
25. Bucala R, Makita Z, Vega G, et al. Modification of low density lipoprotein by advanced glycation end products contributes to the dyslipidemia of diabetes and renal insufficiency. Proc Natl Acad Sci U S A 1994; 91:9441–9445.
26. Lithner F, Asplund K, Eriksson S, et al. Clinical characteristics in diabetic stroke patients. Diabetes Metab 1988; 14:15–19.
27. Pyorala, K. Diabetes and coronary artery disease: what a coincidence? J Cardiovasc Pharmacol 1990; 16:S8–S14.
28. Ruderman NB, Haudenschild C. Diabetes as an atherogenic factor. Prog Cardiovasc Dis 1984; 26:373–412.
29. Mahley RW, Innerarity TL, Weisgraber KN, Oh SY. Altered metabolism (in vivo and in vitro) of plasma lipoproteins after selective chemical modification of lysine residues of the apoproteins. J Clin Invest 1979; 64:743–750.
30. Mahley RW, Innerarity TL, Pitas RE, et al. Inhibition of lipoprotein binding to cell surface receptors of fibroblasts following selective modification of arginyl residues in arginine- rich and B apoproteins. J Biol Chem 1977; 252:7279–7287.

31. Goldstein JL, Ho YK, Basu SK, Brown MS. Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoproteins producing massive cholesterol deposition. Proc Natl Acad Sci U S A 1979; 76:333–337.
32. Fogelman AM, Haberland ME, Seager J, et al. Factors regulating the activities of the low density lipoprotein receptor and the scavenger receptor on human monocyte- macrophages. J Lipid Res 1981; 22:1131–1141.
33. Stitt AW, He C, Friedman S, et al. Elevated AGE-modified ApoB in the sera of euglycemic, normolipidemic patients with atherosclerosis. Mol Med 1997; 3:617–627.
34. Nakamura Y, Horii Y, Nishino T, et al. Immunohistochemical localization of advanced glycosylation end products (AGEs) in coronary atheroma and cardiac tissue in diabetes. Am J Pathol 1993; 143:1649–1656.
35. Sima A, Popov D, Starodub O et al. Pathobiology of the heart in experimental diabetes: immunolocalization of lipoproteins, immunoglobulin G, and advanced glycation end products proteins in diabetic and/or hyperlipidemic hamster. Lab Invest 1997; 77:3–18.
36. Niwa T, Katsuzaki T, Miyazaki S, et al. Immunohistochemical detection of imidazolone, a novel advanced glycation end product, in kidneys and aortas of diabetic patients. J Clin Invest 1997; 99:1272–1280.
37. Horiuchi S, Sano H, Higashi T, et al. Extra- and intracellular localization of advanced glycation end-products in human atherosclerotic lesions. Nephrol Dial Transplant 1996; 11(Suppl 5):81–86.
38. Palinski W, Koschinsky T, Butler SW, et al. Immunological evidence for the presence of advanced glycosylation end products in atherosclerotic lesions of euglycemic rabbits. Arterioscler Thromb Vasc Biol 1995; 15:571–582.
39. Kume S, Takeya M, Mori T, et al. Immunohistochemical and ultrastructural detection of advanced glycation end products in atherosclerotic lesions of human aorta with a novel specific monoclonal antibody. Am J Pathol 1995; 147:654–667.
40. Stern DM, Esposito C, Gerlach H, et al. Endothelium and regulation of coagulation. Diabetes Care 1991; 14:160–166.
41. Kirstein M, Aston C, Hintz R, Vlassara H. Receptor-specific induction of insulin-like growth factor I in human monocytes by advanced glycosylation end product-modified proteins. J Clin Invest 1992; 90:439–446.
42. Vlassara H, Fuh H, Donnelly T, Cybulsky M. Advanced glycation end products promote adhesion molecule (VCAM-1, ICAM-1) expression and atheroma formation in normal rabbits. Mol Med 1995; 1:447–456.
43. Li YM, Mitsuhashi T, Wojciechowicz D, et al. Molecular identity and cellular distribution of advanced glycation endproduct receptors: relationship of p60 to OST-48 and 80K-H membrane proteins. Proc Natl Acad Sci U S A 1996; 93:11047–11052.
44. Stitt AW, He C, Burke G, et al. The advanced glycation end product (AGE) receptor complex: characterisation in micro and macrovascular endothelium [abstract]. Diabetes 1997; 46:53A.
45. Schmidt AM, Yan SD, Wautier JL, Stern D. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ Res 1999; 84:489–497.
46. Schmidt AM, Hasu M, Popov D, et al. Receptor for advanced glycation end products (AGEs) has a central role in vessel wall interactions and gene activation in response to circulating age proteins. Proc Natl Acad Sci U S A 1994; 91:8807–8811.
47. Dobrian A, Lazar V, Tirziu D, Simionescu M. Increased macrophage uptake of irreversibly glycated albumin modified-low density lipoproteins of normal and diabetic subjects is mediated by non-saturable mechanisms. Biochim Biophys Acta 1996; 1317:5–14.
48. Seftel AD, Vaziri ND, Ni Z, et al. Advanced glycation end products in human penis: elevation in diabetic tissue, site of deposition, and possible effect through iNOS or eNOS. Urology 1997; 50:1016–1026.
49. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium dependent vasodilatation in experimental diabetes. J Clin Invest 1991; 87:432–438.
50. Vlassara H, Fuh H, Makita Z, et al. Exogenous advanced glycosylation end products induce complex vascular dysfunction in normal animals: a model for diabetic and aging complications. Proc Natl Acad Sci U S A 1992; 89:12043–12047.
51. Dyck PJ, Hansen S, Karnes J, et al. Capillary number and percentage closed in human diabetic sural nerve. Proc Natl Acad Sci U S A 1985; 82:2513–2517.
52. Vinik AI, Holland MT, Le Beau JM, et al. Diabetic neuropathies. Diabetes Care 1992; 15:1926–1975.
53. Gugliucci A, Bendayan M. Reaction of advanced glycation endproducts with renal tissue from normal and streptozotocin-induced diabetic rats. An ultrastructural study using colloidal gold cytochemistry. J Histochem Cytochem 1995; 43:591–600.
54. Makino H, Shikata K, Hironaka K, et al. Ultrastructure of nonenzymatically glycated mesangial matrix in diabetic nephropathy. Kidney Int 1995; 48:517–526.
55. Pugliese G, Pricci F, Romeo G, et al. Upregulation of mesangial growth factor and extracellular matrix synthesis by advanced glycation end products via a receptor- mediated mechanism. Diabetes 1997; 46:1881–1887.
56. Yamauchi A, Takei I, Makita Z, et al. Effects of aminoguanidine on serum advanced glycation endproducts, urinary albumin excretion, mesangial expansion, and glomerular basement membrane thickening in Otsuka Long-Evans Tokushima fatty rats. Diabetes Res Clin Pract 1997; 34:127–133.
57. Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation end products: biochemical, biologic, and clinical implications for diabetes and aging. Lab Invest 1994; 70:138–151.
58. Stitt AW, Li YM, Gardiner TA, et al. Advanced glycation end products (AGEs) co-localize with AGE receptors in the retinal vasculature of diabetic and of AGE-infused rats. Am J Pathol 1997; 150:523–531.
59. Hammes HP, Wellensiek B, Kloting I, et al. The relationship of glycaemic level to advanced glycation end-product (AGE) accumulation and retinal pathology in the spontaneous diabetic hamster. Diabetologia 1998; 41:165–170.
60. Clements RS, Jr, Robison WG, Jr, Cohen MP. Anti-glycated albumin therapy ameliorates early retinal microvascular pathology in db/db mice. J Diabetes Complications 1998; 12:28–33.
61. Hammes HP, Martin S, Federlin K, et al. Aminoguanidine treatment inhibits the development of experimental diabetic retinopathy. Proc Natl Acad Sci U S A 1991; 88:11555–11558.
62. Kern TS, Engerman RL. Pharmacological inhibition of diabetic retinopathy. Diabetes 2001; 50:1636–1642.
63. Lee AT, Cerami A. Elevated glucose 6-phosphate levels are associated with plasmid mutations in vivo. Proc Natl Acad Sci U S A 1987; 84:8311–8314.
64. Bucala R, Model P, Russel M, Cerami A. Modification of DNA by glucose 6-phosphate induces DNA rearrangements in an Escherichia coli plasmid. Proc Natl Acad Sci U S A 1985; 82:8439–8442.
65. Jacobson EL, Cervantes-Laurean D, Jacobson MK. ADP-ribose in glycation and glycoxidation reactions. Adv Exp Med Biol 1997; 419:371–379.

66. Cervantes-Laurean D, Jacobson EL, Jacobson MK. Glycation and glycoxidation of histones by ADP-ribose. J Biol Chem 1996; 271:10461–10469.
67. Gugliucci A, Bendayan M. Histones from diabetic rats contain increased levels of advanced glycation end products. Biochem Biophys Res Commun 1995; 212:56–62.
68. Mills JL. Malformations in infants of diabetic mothers. Teratology 1982; 25:385–394.
69. Mills JL, Baker L, Goldman AS. Malformations in infants of diabetic mothers occur before the seventh gestational week. Implications for treatment. Diabetes 1979; 28:292–293.
70. Mills JL, Knopp RH, Simpson JL, et al. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. N Engl J Med 1988; 318:671–676.
71. Vlassara H, Brownlee M, Cerami A. Novel macrophage receptor for glucose-modified proteins is distinct from previously described scavenger receptors. J Exp Med 1986; 164:1301–1309.
72. Radoff S, Cerami A, Vlassara H. Isolation of surface binding protein specific for advanced glycosylation end products from mouse macrophage-derived cell line RAW 264.7. Diabetes 1990; 39:1510–1518.
73. Yang Z, Makita Z, Horii Y, et al. Two novel rat liver membrane proteins that bind advanced glycosylation end products: relationship to macrophage scavenger receptor for glucose modified proteins. J Exp Med 1991; 174:515–524.
74. Goh KC, Lim YP, Ong SH, et al. Identification of p90, a prominent tyrosine-phosphorylated protein in fibroblast growth factor stimulated cells, as 80K-H. J Biol Chem 1996; 271:5832–5838.
75. Vlassara H, Li YM, Imani F, et al. Identification of galectin-3 as a high-affinity binding protein for advanced glycation end products (AGE): a new member of the AGE-receptor complex. Mol Med 1995; 1:634–646.
76. Ohgami N, Nagai R, Ikemoto M, et al. CD36, a member of class B scavenger receptor family, as a receptor for advanced glycation end products. J Biol Chem 2001; 276:3195–3202.
77. Takata K, Horiuchi S, Araki N, et al. Endocytic uptake of nonenzymatically glycosylated proteins is mediated by a scavenger receptor for aldehyde-modified proteins. J Biol Chem 1988; 263:14819–14825.
78. Araki N, Higashi T, Mori T, et al. Macrophage scavenger receptor mediates the endocytic uptake and degradation of advanced glycation end products of the Maillard reaction. Eur J Biochem 1995; 230:408–415.
79. Vlassara H, Brownlee M, Manogue KR, et al. Cachectin/TNF and IL-1 induced by glucose- modified proteins: role in normal tissue remodeling. Science 1988; 240:1546–1548.
80. Mackic, JB, Stins M, McComb JG, et al. Human blood-brain barrier receptors for Alzheimer's amyloid-beta 1- 40. Asymmetrical binding, endocytosis, and transcytosis at the apical side of brain microvascular endothelial cell monolayer J Clin Invest 1998, 102:734–743.
81. Sano H, Higashi T, Matsumoto K, et al. Insulin enhances macrophage scavenger receptor- mediated endocytic uptake of advanced glycation end products. J Biol Chem 1998; 273:8630–8637.
82. Horiuchi S, T Higashi, K Ikeda, et al. Advanced glycation end-products and their recognition by macrophage and macrophage-derived cells. Diabetes 1996; 45(Suppl 3):S73–S76.
83. Vlassara H, Brownlee M, Cerami A. Specific macrophage receptor activity for advanced glycosylation end products inversely correlates with insulin levels in vivo. Diabetes 1988; 37:456–461
84. Vlassara H, Moldawer L, Chan C. Macrophage/monocyte receptor for nonenzymatically glycosylated protein is upregulated by cachectin/tumor necrosis factor. J Clin Invest 1989; 84:1813–1820.
85. Vlassara H. Advanced non-enzymatic tissue glycosylation: mechanisms implicated in the complications associated with aging. In: Clegg M, O'Brien S, editors. Molecular biology of aging. New York: Alan R. Liss, Inc.; 1989. pp. 171–185.
86. Radoff S, Vlassara H, Cerami A. Characterization of a solubilized cell surface binding protein on macrophages specific for proteins modified nonenzymatically by advanced glycosylated end products. Arch Biochem Biophys 1998; 263:418–423.
87. Stitt, AW, Burke GA, Chen F, et al. Advanced glycation end-product receptor interactions on microvascular cells occur within caveolin-rich membrane domains. FASEB J 2000; 14:2390–2392.
88. Pugliese G, Pricci F, Iacobini C, et al. Accelerated diabetic glomerulopathy in galectin- 3/AGE receptor 3 knockout mice. FASEB J 2001; 15:2471–2479.
89. He C, Zheng F, Stitt A, et al. Differential expression of renal AGE-receptor genes in NOD mice: possible role in nonobese diabetic renal disease. Kidney Int 2000; 58:5:1931–1940.
90. He C, Stitt A, Striker L, et al. Low expression of AGE-receptor-1 in NOD mouse mesangial cells: possible link to diabetic nephropathy [abstract]. J Am Soc Nephrol 1996; 7:1871A
91. He C, Koschinsky T, Buenting C, Vlassara H. Presence of diabetic complications in type 1 diabetic patients correlates with low expression of mononuclear cell AGE-receptor-1 and elevated serum AGE. Mol Med 2001; 7:159–168.
92. He C, Koschinsky T, Sabol J, et al. Mononuclear (MN) cell AGE receptor-1 (AGE-R1) mRNA expression and its relationship to diabetic complications [abstract]. Diabetes 1997; 46:8A.
93. Kadrofske M, Openo KP, Wang JL. The human LGALS3 (Gelectin-3) gene: determination of the gene structure and functional characterization of the promoter. Arch Biochem Biophys 1998; 349:7–20.
94. Sakai K, Hirai M, Minoshima S, et al. Isolation of cDNAs encoding a substrate for protein kinase C: nucleotide sequence and chromosomal mapping of the gene for a human 80K protein. Geomics 1989; 5(2):309–315.
95. Yamagata T, Tsuru T, Momoi MY, et al. Genome organization of human 48-kDa oligosaccharyltranferase (DDOST). Genomics 1997; 45:535–540.
96. Poirier O., Nicaud V, Vionnet N, et al. Polymorphism screening of four genes encoding advanced glycation end-product putative receptors. Association study with nephropathy in Type 1 diabetic patients. Diabetes 2001; 50:1214–1218.
97. Hudson BI, Strickland MH, Grant PJ. Identification of polymorphisms in the receptor for advanced glycation end products (RAGE) gene. Diabetes 1998; 47:1155–1157.
98. Gardiner TA, Stitt AW, Archer DB. Endocytosis by retinal vascular endothelial cells increases in early diabetes: a quantitative EM study in STZ-diabetic rats. Lab Invest 1995; 72:439–444.
99. Stitt AW, Chakravarthy U, Archer DB Gardiner TA. Increased endocytosis of retinal vascular endothelial cells grown in hyperglycemia is modulated by inhibitors of non- enzymatic glycosylation. Diabetologia 1995; 38:1271–1275.
100. Vlassara H. Recent progress in advanced glycation end products and diabetic complications. Diabetes 1997; 46(Suppl 2):S19–S25.
101. Makita Z, Radoff S, Rayfield EJ, et al. Advanced glycosylation end products in patients with diabetic nephropathy. N Engl J Med 1991; 325:836–842.

102. Makita Z, Bucala R, Rayfield EJ, et al. Reactive glycosylation end products in diabetic uraemia and treatment of renal failure. Lancet 1994; 343:1519–1522.

103. Miyata T, Oda O, Inagi R, et al. beta 2-microglobulin modified with advanced glycation end products is a major component of hemodialysis-associated amyloidosis. J Clin Invest 1993; 92:1243–1252.

104. Miyata T, Inagi R, Iida Y, et al. Involvement of beta 2-microglobulin modified with advanced glycation end products in the pathogenesis of hemodialysis-associated amyloidosis. Induction of human monocyte chemotaxis and macrophage secretion of tumor necrosis factor-alpha and interleukin-1. J Clin Invest 1994; 93:521–528.

105. Dolhofer-Bliesener R, Lechner B, Gerbitz KD. Possible significance of advanced glycation end products in serum in end-stage renal disease and in late complications of diabetes. Eur J Clin Chem Clin Biochem 1996; 34:355–361.

106. Shinohara M, Thornalley PJ, Giardino I, et al. Overexpression of glyoxalase-1 in bovine endothelial cells inhibits intracellular advanced glycation end product formation and prevents hyperglycemia-induced increases in macromolecular endocytosis. J Clin Invest 1998; 101:1142–1147.

107. Li YM, Tan AX, Vlassara H. Antibacterial activity of lysozyme and lactoferrin is inhibited by binding of advanced glycation-modified proteins to a conserved motif. Nat Med 1995; 1:1057–1061.

108. Mitsuhashi T, Li YM, Fishbane S, Vlassara H. Depletion of reactive advanced glycation endproducts from diabetic uremic sera by a lysozyme-linked matrix. J Clin Invest 1997; 100:847–854.

109. Vlassara H, Li J, Bohmart A, Zheng F. Lysozyme (LZ) is secreted by mesangial cells and inhibits glycoxidation-dependent glomerular gene dysregulation in vitro and in vivo: a novel defense mechanism against diabetic nephropathy [abstract]. Diabetes 2000; 49:A161.

110. Zheng, F, Cai W, Mitsuhashi T, Vlassara H. Lysozyme enhances renal excretion of advanced glycation endproducts in vivo and suppresses adverse age-mediated cellular effects in vitro: a potential AGE-sequestration therapy for diabetic nephropathy? Mol Med 2001; 7:737–747.

111. Zheng F, He C, Li J, Vlassara H. In vivo treatment of diabetic mice (NOD and db/db) with lysozyme (LZ) enhances renal clearance of glycoxidation products and prevents albuminuria [abstract]. Diabetes 2000; 49:A161.

112. Lin RY, Reis ED, Dore AT, et al. Lowering of dietary advanced glycation endproducts (AGE) reduces neointimal formation after arterial injury in genetically hypercholesterolemic mice. Atherosclerosis 2002; 163:303–311.

113. Vlassara H, Cai W, Crandall J, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci U S A 2002; 99:15596–15601.

114. Brownlee M, Vlassara H, Kooney A, et al. Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking. Science 1986; 232:1629–1632.

115. Giardino I, Fard AK, Hatchell DL, Brownlee M. Aminoguanidine inhibits reactive oxygen species formation, lipid peroxidation, and oxidant-induced apoptosis. Diabetes 1998; 47:1114–1120.

116. Panagiotopoulos S, O'Brien RC, Bucala R, et al. Aminoguanidine has an anti-atherogenic effect in the cholesterol-fed rabbit. Atherosclerosis 1998; 136:125–131.

117. Nichols K, Mandel TE. Advanced glycosylation endproducts in experimental murine diabetic nephropathy: effect of islet isografting and of aminoguanidine. J Lab Invest 1989; 60:486–491.

118. Ellis EN, Good BH. Prevention of glomerular basement membrane thickening by aminoguanidine in experimental diabetes mellitus. Metabolism 1991; 40:1016–1019.

119. Ido Y, Chang K, Ostrow E, et al. Aminoguanidine prevents regional blood flow increases in streptozotocin-diabetic rats [abstract]. Diabetes 1990; 39:93A.

120. Soulis Liparota T, Cooper M, Papazoglou D, et al. Retardation by aminoguanidine of development of albuminuria, mesangial expansion, and tissue fluorescence in streptozocin-induced diabetic rat. Diabetes 1991; 40:1328–1334.

121. Edelstein D, Brownlee M. Mechanistic studies of advanced glycosylation end product inhibition by aminoguanidine. Diabetes 1992; 41:26–28.

122. Cho HK, Kozu H, Peyman GA, et al. The effect of aminoguanidine on the blood-retinal barrier in streptozocin-induced diabetic rats. Ophthalmic Surg 1991; 22:44–47.

123. Nakamura S, Makita Z, Ishikawa S, et al. Progression of nephropathy in spontaneous diabetic rats is prevented by OPB-9195, a novel inhibitor of advanced glycation. Diabetes 1997; 46:895–899.

124. Mitsuhashi T, Li YM, Fishbane S, Vlassara H. Depletion of reactive advanced glycation endproducts from diabetic uremic sera using a lysozyme-linked matrix. J Clin Invest 1997; 100:847–854.

125. Vasan S, Zhang X, Zhang X, et al. An agent cleaving glucose-derived protein crosslinks in vitro and in vivo. Nature 1996; 382:275–278.

126. Drickamer K. Diabetes: breaking the curse of the AGEs. Nature 1996; 382:211–212.

127. Wolffenbuttel BH, Boulanger CM, Crijns FR et al. Breakers of advanced glycation end products restore large artery properties in experimental diabetes. Proc Natl Acad Sci U S A 1998; 95:4630–4634.

Grand Rounds

Primary Biliary Cirrhosis:

A Mount Sinai Perspective

Nancy Bach, M.D.[1], and Joseph A. Odin, M.D., Ph.D.[2]

Abstract

Individuals afflicted with primary biliary cirrhosis (PBC) first undergo chronic, nonsuppurative destruction of their intrahepatic bile ducts, eventually leading to cirrhosis. Over nearly 50 years, many faculty members at the Mount Sinai School of Medicine, including Dr. Hans Popper and Dr. Fenton Schaffner, have made important contributions to our understanding of the natural history and histopathologic evolution of PBC. And today, many patients with PBC continue to be cared for at Mount Sinai. In the absence of a cure for the disease, these patients continue to be enrolled in clinical trials and, when necessary, in the Mount Sinai liver transplant program. The establishment of the Center for the Study of Primary Biliary Cirrhosis at Mount Sinai, supported by the Artzt Family Foundation Trust, has enabled the faculty to expand both clinical and basic science initiatives related to primary biliary cirrhosis. Several of these new initiatives are described below and placed in the context of our current understanding of the immunopathogenesis of PBC.

Key Words: Primary biliary cirrhosis, methotrexate, celiac disease, apoptosis, cholangiocytes, autoantibody, protein oxidation, pyruvate dehydrogenase, genetics.

Introduction

PRIMARY BILIARY CIRRHOSIS (PBC) is a potentially fatal chronic liver disease primarily affecting women and is typically diagnosed during the fifth decade of the person's life. PBC is characterized by the chronic, nonsuppurative destruction of intrahepatic bile duct epithelial cells (cholangiocytes) and by high titers of antimitochondrial antibodies (AMA) (1). The disease is often detected incidentally in its asymptomatic stage when elevated serum alkaline phosphatase levels are noted. Fatigue and pruritus are the most common presenting symptoms. Although it is an uncommon disease, PBC is a frequent indication for liver transplantation among women. Approximately 70% of patients also have salivary gland involvement (2).

Prior to the era of orthotopic liver transplantation, PBC was often fatal. In recent years, treatment with ursodeoxycholic acid (UDCA) has been shown to slow progression of the disease and delay or obviate the need for liver transplantation. A number of research avenues are being pursued in the hope of further slowing down the progression of the disease or curing it, thereby eliminating any need for liver transplantation. A number of present and past investigators at the Mount Sinai School of Medicine have contributed to our understanding of PBC. In this article, we will briefly outline the current state of knowledge regarding PBC, while focusing on a number of ongoing PBC-related research efforts at Mount Sinai.

Disease Course

The course of PBC from its often long asymptomatic phase to possible liver failure is somewhat predictable. For a complete review, see the landmark paper by Shapiro et al. (3)

---

[1] Assistant Clinical Professor and [2] Assistant Professor, Division of Liver Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Joseph A. Odin, M.D., Ph.D., Division of Liver Diseases, Department of Medicine, Box 1123, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Supported by the Artzt Family PBC Foundation, a Schering/AASLD Advanced Hepatology Fellowship Award, and an NIH K08 Award (NIDDK).

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY, on November 14, 2000, and updated as of December 2002.

studying the natural history of this disease. In their study of the disease course of PBC, patients were divided into a stable phase and an accelerated phase, based on the level of bilirubin. Though the Mayo Risk Score (4) has somewhat supplanted the bilirubin level as the sole determinant of prognosis, the observations made several decades ago still remain valid. Shapiro et al. noted that most people with PBC remain in the so-called stable phase of disease, during which the bilirubin remains in the normal range, for a prolonged period of time. Patients then enter into an accelerated phase of disease, at which time the bilirubin rises. When two consecutive bilirubin levels are in excess of 2 mg/dL, average survival time is four years. Since this original study (3), the time spent by most patients in the stable phase of the disease has increased to more than 20 years. Part of this increase may be due to earlier recognition and diagnosis of the disease.

Current Medical Treatment

The ultimate goal of therapy in PBC, naturally, is to cure the disease. While there is as yet no cure for PBC, current treatments do slow the disease's progression. Ursodeoxycholic acid is now the mainstay of therapy for PBC. Several large, randomized controlled trials using UDCA have found its use to be beneficial (5–8). With treatment failure and/or bilirubin levels as end points, UDCA had a statistically significant beneficial effect on survival. In the study by Combes et al. (5), this benefit was seen only for those patients whose pretreatment serum bilirubin levels were less than 2 mg/dL. Two studies addressed the optimal dosing of UDCA in PBC. Both studies found that 13–15 mg/kg/day provided the greatest benefit in terms of UDCA enrichment of bile acids and improvement in Mayo Risk Score, total bilirubin, alkaline phosphatase and gamma-glutamyl-transferase (GGT) (9, 10).

In a recent paper by Poupon and the UDCA-PBC study group, an analysis of 10-year survival found that survival rates of non-cirrhotic PBC patients were comparable to those of an age- and sex-matched control population of persons without PBC (11). However, for the group of patients who had PBC with cirrhosis on biopsy, survival was decreased. Treatment with UDCA improved survival rates in both groups (11). A number of drugs including azathioprine, chlorambucil, cyclosporine, penicillamine, and prednisolone have been tested and found to be either too toxic or ineffective in treating the disease (12).

Effect of Methotrexate on the Course of PBC

In the late 1980s, preliminary studies (13) suggested that methotrexate might be of benefit in treating PBC. In the late 1980s, 110 patients initiated treatment with weekly methotrexate. Accordingly, with IRB approval, we reviewed the data recorded in the charts to assess the effect of methotrexate on survival without liver transplant, Mayo Risk Score and various biochemical and histologic parameters (14). We also assessed how well this drug was tolerated by individuals with PBC. Patients were treated with 15 mg of methotrexate weekly. As the benefits of UDCA became more evident in the early 1990s, UDCA was either initiated or resumed for most patients. Pruritus and osteoporosis were treated according to the individual needs of the patients.

Of the original 110 patients who began therapy, only 57 were still taking methotrexate regularly at 5 years. Of the 53 patients who discontinued treatment prematurely, 27 patients did so because of adverse drug effect which included nausea, chronic cough or shortness of breath, ulcerative stomatitis, alopecia and accelerated bone loss. Thirteen of these 53 patients discontinued the methotrexate and received a liver transplant. MTX was discontinued in 6 individuals who moved out of the area and were no longer under our care. Four patients were diagnosed as having a non-hepatic carcinoma. One patient was reported to have become pregnant after starting MTX. No further follow-up information is available except that she no longer continued on therapy at this institution. One patient had esophageal varices. One patient was noncompliant.

Of the 57 patients who completed at least 5 years of treatment, the effect of methotrexate on several prognostic markers and laboratory was evaluated. Table 1 shows the median slope values and 95% confidence intervals. Because age is a variable used in calculating the Mayo Risk Score, age alone would cause an increase in Mayo Risk Score, even if all other parameters were to remain the same. Therefore, a separate calculation for Mayo Risk Score was performed, excluding age. A positive slope reflects an increase in a value with time, and a negative slope indicates a decrease in a value.

Whether calculated with or without age, Mayo Risk Score increased during treatment with MTX and UDCA. While not statistically sig-

TABLE 1
Comparison of Treatment with Methotrexate Alone or with Methotrexate and Ursodeoxycholate

Endpoint	MTX Median Slope	[95% CI]	p	MTX/UDCA Median Slope	[95% CI]	p
MRS	0.06	[–0.007, 0.11]	0.07	0.09	[0.06, 0.11]	0.0001
MRS (w/o age)	0.02	[–0.05, 0.09]	0.54	0.05	[0.03, 0.07]	0.0001
Total bilirubin	0.01	[–0.02, 0.04]	0.31	0.01	[–0.004, 0.02]	0.26
Alk. Phos.	–0.07	[–0.44, –0.001]	0.03	–0.07	[–0.13, –0.05]	0.0001
GGT	–0.08	[–0.21, 0.15]	0.41	–0.10	[–0.22, –0.04]	0.0001

* A positive slope represents an increase in the endpoint's value. ** A negative slope represents a decrease. MRS = Mayo Risk Score.

nificant, a rising trend was also noted for Mayo Risk Score and bilirubin during the time the patients received methotrexate alone. Because the study was carried out for only five years, a change in bilirubin would not have been expected. Interestingly, there was a statistically significant decrease in alkaline phosphatase during treatment with methotrexate alone and in combination with UDCA, and for GGT during combination therapy. During treatment with methotrexate alone, GGT activity decreased, though the decrease was not statistically significant.

Forty-nine of the 57 patients had biopsies performed before and after five years of treatment. In 63% of the cases, methotrexate did not alter the extent of portal fibrosis and portal inflammation. Portal fibrosis progressed in 25% of the cases and diminished in 12%. Lobular inflammation remained unchanged in 61% and bile duct loss remained unchanged in 53%. These changes may have been the result of sampling differences.

The second part of our study analyzed survival. Through collaboration with the Mayo Clinic, we were able to construct a historical control group based on data from a previously published placebo-controlled trial of UDCA. These data allowed us to determine if methotrexate had a beneficial effect on survival in those patients who did not receive a transplant, despite our findings that the disease had progressed with treatment. Using a Cox proportional hazard model controlling for Mayo Risk Score and the use of ursodeoxycholic acid, treatment failure (defined as death or liver transplantation) was assessed based on Mayo Risk Score and ursodeoxycholic acid and methotrexate use. As expected, a rising Mayo Risk Score was associated with an increased risk of death or the need for liver transplant (p=0.0001). The use of UDCA significantly decreased the likelihood of death or transplant by 16% (p=0.006) (14). Methotrexate use did not cause a statistically significant alteration in outcome, though the trend was toward an adverse outcome. From our study, we therefore concluded that PBC progresses despite therapy with methotrexate. Methotrexate did not improve survival or prevent complications or the need for transplant, and long-term treatment with methotrexate was not well tolerated.

Immunopathogenesis of Autoantibody Production in PBC

Gershwin and others (15 – 17) have determined that more than 90% of patients with PBC produce autoantibodies against specific regions of the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2), a ubiquitously expressed mitochondrial matrix protein associated with the inner mitochondrial membrane. Autoreactive T cells specific for PDC-E2 self-peptides from the same region recognized by PBC patient autoantibodies have also been isolated from patients with PBC (18, 19). There is no direct evidence that these autoantibodies or autoreactive T cells are pathogenic. Indeed, the auto-antibodies and autoreactive T cells cross-react to varying extents with xenobiotic sources of pyruvate dehydrogenase and peptides respectively, including bacterial sources (20, 21). Mason et al. (22) have even identified a virus that may be a source of cross- reactive antigen. In a proposed mouse model of PBC, immunization with bovine pyruvate dehydrogenase complex (PDC) eventually leads to loss of tolerance to self (mouse)-PDC and biliary inflammation (23). Consequently, uncertainty exists with regard to the source of the immunogen responsible for the activation of autoreactive B and T cells in patients with PBC. The results of ongoing studies at Mount Sinai investigating apoptotic cholangiocytes as a potential source of immunogenic PDC-E2 are discussed below.

Antibodies produced in response to a specific immunogen may be capable of recognizing several antigens that share an epitope in common with the original immunogen. Epitope analysis and autoantibody titration experiments have helped define the potential immunogenicity of different sources and forms of PDC-E2. The PDC-E2 epitope recognized by anti-PDC-E2 autoantibodies from patients with PBC is a very specific region within the inner lipoyl domain. The epitope appears to be conformational in nature, since no short peptide sequence completely inhibits binding to the inner lipoyl domain (17). The outer lipoyl domain is also recognized, but this may represent cross-reactivity, since the sequences are similar and both contain lipoyllysine residues (lipoic acid covalently bound to a lysine side-chain), which are important in antibody recognition (24). Other common PBC antigens also contain these uncommon lipoyllysine residues. Lipoic acid contains a dithiol group, and early studies of purified PDC and PDC-E2 indicated that PBC patient sera preferentially recognized PDC-E2 to which sulfhydryl reducing agents had been added (25).

The most tantalizing finding with regard to the source and identity of the immunogenic form of PDC-E2 was obtained by immunohistochemical staining of liver biopsy specimens from patients with PBC autoantibodies. Increased staining by PBC patient autoantibodies was specifically noted in the cholangiocytes of patients with PBC (26, 27). Most of the additional staining was near the apical border of the cell and significantly was non-mitochondrial. *In situ* hybridization of PDC-E2 mRNA in PBC patient cholangiocytes actually showed decreased levels of message in the cholangiocytes of patients with PBC (28). There was no evidence of decreased PDC-E2 protein degradation, which typically accounts for increased levels of the autoreactive epitope. The cause of this abnormal pattern of staining remains unresolved.

Effect of Apoptosis on the Major PBC Autoantigen

In other autoimmune diseases, cells that have undergone apoptosis (programmed cell death) have been proposed as a source immunogen responsible for autoantibody production (29, 30), since unique forms of many self-proteins are present in apoptotic cells (31, 32). A high percentage of autoantigens, unlike non-autoantigens, are specifically cleaved by caspases and become concentrated in cytoplasmic surface blebs and apoptotic bodies during apoptosis (33). Other autoantigens are phosphorylated during apoptosis (30). The immune response to unique proteins within apoptotic cells appears to vary depending on the local environment. Apoptosis of cholangiocytes is increased in patients with PBC (34–36). However, the presence of distinct forms of PBC autoantigens in apoptotic cells has not been reported. Therefore, we examined the effect of apoptosis on PDC-E2 in cholangiocytes and non-cholangiocytes to determine if cholangiocyte apoptosis might have a unique effect on PDC-E2.

Staining of untreated control cells (Fig. 1) with PBC patient antisera mono-specific for PDC-E2 resulted in a mitochondrial pattern (Fig. 1I, 1K, 1M, and 1O) that was identical to that of mitochondrial cytochrome C oxidase subunit 1 (Cox 1) (data not shown). Following irradiation with ultraviolet B light (UV-B), staining of PDC-E2 in apoptotic normal rat cholangiocytes (NRC) and salivary gland epithelial cells (HSG) (Figs. 1J & 1L, respectively) remained punctate, peri-nuclear, and colocalized with Cox 1 (data not shown). Surprisingly, staining of PDC-E2 in apoptotic HeLa, Jurkat, and Caco-2 cells (Fig. 1N, 1P, data not shown; apoptotic cells are labeled with a white star) was undetectable, though Cox 1 staining persisted (data not shown). In contrast, UV-B irradiated HeLa, Jurkat, and Caco-2 cells that were not yet apoptotic (unlabeled cells) stained strongly for PDC-E2 (Fig. 1N, 1P, data not shown). Loss of PDC-E2 staining in apoptotic cells was also observed after staurosporine treatment of HeLa and Caco-2 cells, and Fas ligation of Jurkat T cells (data not shown). In conjunction with persistent staining of PDC-E2 in apoptotic normal rat cholangiocytes (NRC) after treatment with staurosporine (data not shown), these results indicate that loss of PDC-E2 staining following apoptosis is a common, but not universal, occurrence.

We investigated the cause of the specificity of PDC-E2 recognition of this cell type in apoptotic cells. Decreases in the cellular sulfhydryl redox potential during apoptosis have been reported for several cell types. Since the antigenic epitope of PDC-E2 contains sulfhydryl groups, we analyzed the effect of sulfhydryl-reducing agents on autoantibody recognition of PDC-E2 in apoptotic cell lysates. In the absence of dithiothreitol (DTT) addition, blotting of PDC-E2 was substantially decreased in lysates of apoptotic HeLa (Fig. 2), but not in apoptotic NRC or human salivary gland (HSG) (Fig. 2).

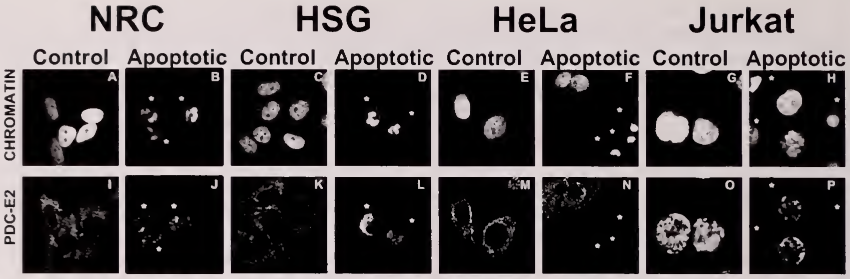

Fig. 1. A–H. Confocal images of control and apoptotic cells stained with DAPI to detect the condensed nuclear chromatin characteristic of apoptotic cells and PBC patient antiserum mono- specific for pyruvate dehydrogenase complex-E2 (PDC-E2) (I–P). A fluorescein isothiocyanate (FITC)-conjugated anti-human immunoglobulin G (IgG) secondary was used for detection of autoantibody binding. Apoptotic cells are labeled with white stars. In apoptotic cells, staining of PDC-E2 is present only in normal rat cholangiocyte (NRC) (J) and human salivary gland (HSG) (L). Representative images are shown. Original magnification was 100X.

The apoptotic fragment of the caspase substrate, poly-ADP ribose polymerase (PARP), is detected in all apoptotic lysates, regardless of oxidative state. Equivalent autoantibody recognition of PDC-E2 in reduced lysates of control and apoptotic cells excludes degradation as a potential mechanism of decreased recognition of PDC-E2 in HeLa. Conversely, the addition of glutathione disulfide (GSSG), a sulfhydryl-oxidizing agent, to lysates of both apoptotic NRC and control HeLa (data not shown) prior to sodium dodecyl sulfate- polyacrylamide gel electrophoresis (SDS-PAGE) abrogated blotting of PDC-E2.

In titration experiments using antiserum from four different patients with PBC, the difference in autoantibody recognition of PDC-E2 in GSSG- versus DTT-treated lysates of NRC ranged from 100- to 1000-fold (data not shown). The electrophoretic mobility and detection levels of [S^{35}Met]-labeled PDC-E2 immunoprecipitated from control cell lysate were not significantly different whether GSSG or DTT was added prior to SDS-PAGE (data not shown). Thus, by both immunostaining and immunoblotting, PBC patient autoantibody detection of the antigenic epitope of PDC-E2 following apoptosis was limited to cholangiocytes and salivary gland epithelial cells. Addition of sulfhydryl oxidizing agents to lysates eliminated PBC autoantibody recognition.

These studies indicated that the conformational form of PDC-E2 present in apoptotic cells varies by cell type. The sulfhydryl redox state of the cell types following apoptosis determined which form was present. The reduced form present in apoptotic cholangiocytes and salivary gland epithelial cells was recognized by PBC patient autoantibodies, while the oxidized form present in other apoptotic cell types was not recognized. Considering that increased numbers of apoptotic cholangiocytes and salivary gland cells are observed in patients with PBC, selective autoantibody recognition of the form of PDC-E2 present in these apoptotic cells strongly suggests that apoptotic cholangiocytes and salivary gland cells are the source of PDC-E2 responsible for anti-PDC-E2 autoantibody production (Fig. 3). The lack of recognition by autoantibodies in the other apoptotic cell types indicates that they cannot be sources of PDC-E2 responsible for anti- PDC-E2 antibody production in all cells.

Genetic Associations

Substantial evidence suggests that an external trigger may initiate the disease in an otherwise susceptible individual. Evidence for the genetic susceptibility to the disease includes the disease's loose associations with various human leukocyte antigen (HLA) markers and an increased prevalence of familial PBC. There has also been a report of an inherited sulfoxidation disorder in PBC patients (37). Several genes and HLA patterns have been reported to be associated with PBC. The significance of these associations remains unclear. Several groups have found that having HLA DR8 increases the risk of PBC two- to seven-fold (38). This gene, however, is neither necessary nor sufficient to cause PBC. In the Japanese population, another

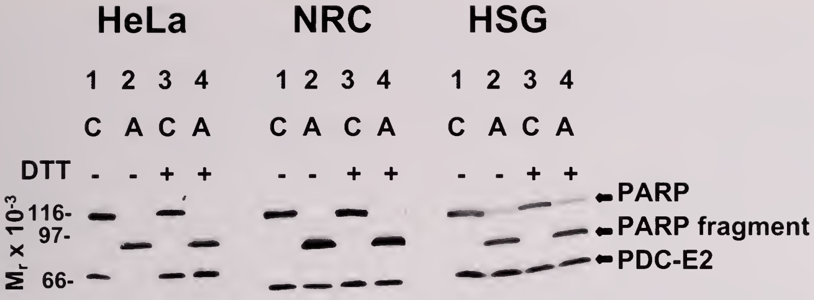

Fig. 2. Immunoblots of lysates from HeLa cells (left panel), normal rat cholangiocytes (NRC) (middle panel) and human salivary gland cells (HSG) (right panel) were incubated with systemic lupus erythematosus (SLE) patient antiserum (top row) specific for poly-ADP ribose polymerase (PARP) (116 kDa), and PBC patient antiserum (bottom row) specific for pyruvate dehydrogenase complex-E2 subunit (PDC-E2) (human: 72 kDa; rat: 66 kDa). 80 mg of protein was loaded in each lane with or without 5 mM dithiothreitol (DTT). The PARP cleavage fragment (89 kDa) is present in all apoptotic lysates. Note the lack of PDC-E2 blotting only in the non-reduced, apoptotic HeLa lysate (lane 2) which excludes degradation as a potential mechanism for its absence in HeLa cells. C = control; A = apoptotic.

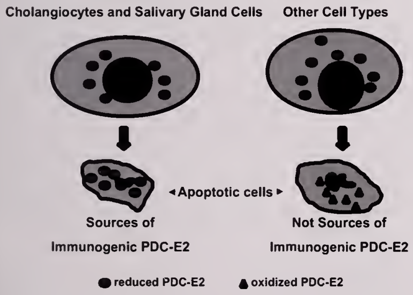
Cholangiocytes and Salivary Gland Cells
Other Cell Types
Apoptotic cells
Sources of Immunogenic PDC-E2
Not Sources of Immunogenic PDC-E2
reduced PDC-E2
oxidized PDC-E2

Fig. 3. Postulated immunogenicity of different non-apoptotic and apoptotic cell types. PBC patient autoantibodies recognize PDC-E2 in all non-apoptotic cells. Recognition in apoptotic cells is specific to cholangiocytes and salivary gland cells.

genotype, DP81*0501, was found to be strongly associated with PBC, although this finding has not been confirmed in Caucasian populations (39). Other associations such as tumor necrosis factor (TNF) alpha and cytotoxic lymphocyte antigen 4 polymorphisms have been less consistent observations (40, 41).

Several years ago, we systematically reviewed the family histories of PBC patients followed in our practice. Of the 564 patients identified, only 405 had sufficient family history available, including data on the parents, siblings and children of the patient, to be included in our review. We identified 26 patients with PBC who had at least one family member with the disease. Using this information, we estimated the prevalence of the disease to be 6420 per 100,000. Seventeen families had more than one family member with documented PBC. Several families had more than two affected family members. The most common relationships were either mother and daughters or sisters.

In order to avoid duplication, we performed a separate calculation excluding those family members who were already patients in our practice. With this exclusion, the prevalence of the disease was 4282 per 100,000 (42). These figures greatly exceed the Mayo Clinic's recent prevalence estimate of 38 cases of PBC per 100,000 individuals in the general population (43). Since our study, several groups have confirmed the increased familial prevalence of this disease (Table 2) (44–46). Though each of the studies is fraught with errors that might either overestimate or underestimate the disease's prevalence, most investigators recognize an increased familial prevalence of this disease.

Association with Autoimmune Diseases

Several autoimmune diseases have been reported to occur with greater frequency in patients with PBC (2). Schaffner and co-workers at Mount Sinai in the late 1970s reported some of the original data establishing an association between thyroid disease and PBC (47). Though the exact percentage of patients with thyroid disease is not known, clearly there is an increased preva-

TABLE 2

Percentage of Patients with PBC Who Have a Relative with PBC

Author (ref.)	Affected Relative (%)
Jones et al. (44)	0.7 (1st degree only)
Brind et al. (45)	1.3
Bach and Schaffner (41)	4.3
Tsuji et al. (43)	5.1

lence of thyroid disease in PBC. Careful screening of PBC patients finds that as many as 72% of those with PBC have Sjögren's disease. Scleroderma has also been associated with PBC and as many as 20% of patients with PBC have joint problems, with a small percentage having rheumatoid arthritis. An association between PBC and celiac disease has also been appreciated for years (48), but controversy exists regarding the prevalence of celiac disease in PBC patients.

Recently five European groups (49–53) have reported celiac disease prevalence rates in patients with PBC ranging from 0–20% (Table 3). This led to our ongoing investigation to determine the prevalence of celiac disease in North American patients with PBC. Titers of various autoantibodies associated with celiac disease are being measured in PBC patients, in collaboration with the Mayo Clinic, Rochester, MN. We anticipate testing more than 300 PBC patients. Preliminary data is available on the first 78 patients (Table 4). Endomysial antibodies were found in 3% and tissue transglutaminase antibodies-IgA in 16% of the patients tested. The literature suggests that these markers are both very sensitive and specific for celiac disease (54). Further exploration of these findings is necessary. Unanswered questions about PBC and celiac disease include: (a) the true prevalence of the disease in North American patients with PBC; (b) the sensitivity and specificity of the various autoantibodies in patients with PBC; and (c) the role that celiac disease may play in causing complications of PBC such as hepatic osteodystrophy.

TABLE 3

Prevalence of Celiac Disease in Patients with PBC

Author (ref.)	Country	n	Prevalence (%)
Kingham and Parker (45)	United Kingdom	67	6
Dickey et al. (49)	Ireland	57	11
Bardella et al. (50)	Italy	65	0
Fidler et al. (51)	United Kingdom	87	2
Niveloni et al. (52)	Argentina	10	20

TABLE 4

Prevalence of Celiac Disease-Associated Autoantibodies in Patients with PBC

Autoantibody Specificity	Isotype	Positive (n)	Percentage (total n = 78)
Gliadin	IgA	9	12
Gliadin	IgG	5	6
Endomysium	Ig	2	3
Tissue transglutaminase	IgA	16	20
Tissue transglutaminase	IgG	32	41

Conclusion

In summary, the outlook for patients with PBC has improved, with patients living longer, more comfortable lives. While the pathogenesis of PBC remains unclear, recent discoveries have increased our understanding of this disease and may lead to novel treatments to augment ursodeoxycholate therapy. With the establishment of the Center for the Study of Primary Biliary Cirrhosis, it is clear that research at Mount Sinai will continue to contribute significantly to this process.

References

1. Kaplan MM. Primary biliary cirrhosis. N Engl J Med 1996; 335(21):1570–1580.
2. Culp KS, Fleming CR, Duffy J, et al. Autoimmune associations in primary biliary cirrhosis. Mayo Clin Proc 1982; 57:365–370.
3. Shapiro, JM, Smith H, Schaffner F. Serum bilirubin: a prognostic factor in primary biliary cirrhosis. Gut 1979; 20:137–140.
4. Dickson ER, Grambsch PM, Fleming TR, et al. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989; 10:1–7.

5. Combes B, Carithers RL, Jr., Maddrey WC, et al. A randomized, double blind placebo controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1995; 22:759–66.
6. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. N Engl J Med 1994; 330:1342–1347.
7. Heathcote EJ, Cauch-Dudek K, Walker V, et al.The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994; 19:1149–1156.
8. Lindor KD, Dickson ER, Baldus WP, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 1994; 106:1284–1290.
9. Verma A, Jazrawi RP, Ahmed HA, et al. Optimum dose of ursodeoxycholic acid in primary biliary cirrhosis. Eur J Gastroenterol Hepatol 1999; 11:1069–1076.
10. Angulo P, Dickson ER, Therneau TM, et al. Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: a randomized trial. J Hepatol 1999; 30:830–835.
11. Poupon RE, Bonnand AM, Chretien Y, Poupon R. Ten-year survival in ursodeoxycholic acid- treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. Hepatology 1999; 29:1668–1671.
12. Poupon R, Poupon RE. Treatment of primary biliary cirrhosis [review]. Baillieres Best Pract Res Clin Gastroenterol 2000; 14(4):615–628.
13. Kaplan MM, Knox TA. Treatment of primary biliary cirrhosis with low-dose methotrexate. Ann Intern Med 1988; 109:429–430.
14. Bach N, Bodian C, Bodenheimer H, Jr., et al. Methotrexate therapy for primary biliary cirrhosis. Am J Gastroenterol 2003; 98:1–7.
15. Gershwin ME, Mackay IR, Sturgess A, Coppel RL. Identification and specificity of a cDNA encoding the 70 kd mitochondrial antigen recognized in primary biliary cirrhosis. J Immunol 1987; 138:3525–3531.
16. Yeaman SJ, Fussey SP, Danner DJ, et al. Primary biliary cirrhosis: identification of two major M2 mitochondrial autoantigens. Lancet 1988; 1:1067–1070.
17. Surh CD, Coppel R, Gershwin ME. Structural requirement for autoreactivity on human pyruvate dehydrogenase-E2, the major autoantigen of primary biliary cirrhosis. Implication for a conformational autoepitope. J Immunol 1990; 144:3367–3374.
18. Van de Water J, Ansari AA, Surh CD, et al. Evidence for the targeting by 2-oxo- dehydrogenase enzymes in the T cell response of primary biliary cirrhosis. J Immunol 1991; 146:89–94.
19. Jones DE, Palmer JM, Yeaman SJ, et al. T cell responses to natural human proteins in primary biliary cirrhosis. Clin Exp Immunol 1997; 107:562–568.
20. Teoh KL, Mackay IR, Rowley MJ, Fussey SP. Enzyme inhibitory autoantibodies to pyruvate dehydrogenase complex in primary biliary cirrhosis differ for mammalian, yeast and bacterial enzymes: implications for molecular mimicry. Hepatology 1994; 19(4):1029–1033.
21. Shimoda S, Nakamura M, Shigematsu H, et al. Mimicry peptides of human PDC-E2 163-176 peptide, the immunodominant T-cell epitope of primary biliary cirrhosis. Hepatology 2000; 31:1212–1216.
22. Mason A, Xu L, Guo L, et al. Detection of retroviral antibodies in primary biliary cirrhosis and other idiopathic biliary disorders. Lancet 1998; 351:1620–1624.
23. Jones DE, Palmer JM, Yeaman SJ, et al. T cell responses to natural human proteins in primary biliary cirrhosis. Clin Exp Immunol 1997; 107:562–568.
24. Quinn J, Diamond AG, Palmer JM, et al. Lipoylated and unlipoylated domains of human PDC-E2 as autoantigens in primary biliary cirrhosis: significance of lipoate attachment. Hepatology 1993; 18:1384–1391.
25. Mendel-Hartvig I, Nelson BD, Loof L, et al. Primary biliary cirrhosis: further biochemical and immunological characterization of mitochondrial antigens. Clin Exp Immunol 1984; 62:371–379.
26. Van de Water J, Turchany J, Leung PS, et al. Molecular mimicry in primary biliary cirrhosis. Evidence for biliary epithelial expression of a molecule cross-reactive with pyruvate dehydrogenase complex-E2. J Clin Invest 1993; 91(6): 2653–2664,
27. Joplin R, Wallace LL, Johnson GD, et al. Subcellular localization of pyruvate dehydrogenase dihydrolipoamide acetyltransferase in human intrahepatic biliary epithelial cells. J Pathol 1995; 176(4):381–390.
28. Harada K, Van de Water J, Leung PS, et al. In situ nucleic acid hybridization of pyruvate dehydrogenase complex-E2 in primary biliary cirrhosis: pyruvate dehydrogenase complex- E2 messenger RNA is expressed in hepatocytes but not in biliary epithelium. Hepatology 1997; 25:27–32.
29. Levine JS, Koh JS. The role of apoptosis in autoimmunity: immunogen, antigen and accelerant. Semin Nephrol 1999; 19:34–47.
30. Utz PJ, Hottelet M, Schur PH, Anderson P. Proteins phosphorylated during stress-induced apoptosis are common targets for autoantibody production in patients with systemic lupus erythematous. J Exp Med 1997; 185(5):843–854.
31. Casciola-Rosen LA, Anhalt GJ, Rosen A. DNA-dependent protein kinase is one of a subset of autoantigens specifically cleaved early during apoptosis. J Exp Med 1995; 182:1625–1634.
32. Casciola-Rosen L, Andrade F, Ulanet D, et al. Cleavage by granzyme B is strongly predictive of autoantigen status: implications for initiation of autoimmunity. J Exp Med 1999; 190:815–826.
33. Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targeted in systemic lupus erythematous are clustered in two populations of surface structures on apoptotic keratinocytes. J Exp Med 1994; 179:1317–1330.
34. Harada K, Ozaki S, Gershwin ME, Nakanuma Y. Enhanced apoptosis relates to bile duct loss in primary biliary cirrhosis. Hepatology 1997; 26(6):1399–1405.
35. Koga H, Sakisaka S, Ohishi M, et al. Nuclear DNA fragmentation and expression of Bcl-2 in primary biliary cirrhosis. Hepatology 1997; 25(5):1077–1084.
36. Graham AM, Dollinger MM, Howie SE, Harrison DJ. Bile duct cells in primary biliary cirrhosis are ‘primed’ for apoptosis. Eur J Gastroenterol Hepatol 1998; 10(7):553–537.
37. Olumo AM, Vickers CR, Waring RH, et al. High incidence of poor sulfoxidation in patients with primary biliary cirrhosis. N Engl J Med; 318:1089–1092.
38. Gregory WL, Mehal W, Dunn AN, et al. Primary biliary cirrhosis: contribution of HLA class II allele DR8. Q J Med 1993; 86:393–399.
39. Seki T, Kiyosawa K, Ota M, et al. Association of primary biliary cirrhosis with human leukocyte antigen DPB1*0501 in Japanese patients. Hepatology 1993; 18:73–78.
40. Gordon MA, Oppenheim E, Camp NJ, et al. Primary biliary cirrhosis shows association with genetic polymorphism of tumour necrosis factor alpha promotor region. J Hepatol 1999; 31:242–247.
41. Agarwal K, Jones DEJ, Bassendine MF. Genetic susceptibility to primary biliary cirrhosis. Eur J Gastroenterol Hepatol 1999; 11:603–606.

42. Bach N, Schaffner F. Familial primary biliary cirrhosis. J Hepatol 1994; 20:698–701.
43. Kim WR, Lindor KD, Locke GR, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. Gastroenterology 2000; 119:1631–1636.
44. Tsuji K, Watanabe Y, Van de Water J, et al. Familial primary biliary cirrhosis in Hiroshima. J Autoimmun 1999; 13:171–178.
45. Jones DE, Watt FE, Metcalf JV, et al. Familial primary biliary cirrhosis reassessed: a geographically-based population study. J Hepatol 1999; 30:402–407.
46. Brind AM, Bray GP, Portmann BC, Williams RF. Prevalence and pattern of familial disease in primary biliary cirrhosis. Gut 1995; 36:615–617.
47. Schussler GC, Schaffner F, Korn F. Increased serum thyroid hormone binding and decreased free hormone in chronic liver disease. N Engl J Med 1978; 299:510–515.
48. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology 2000; 31:1005–1013.
49. Kingham JG, Parker DR. The association between primary biliary cirrhosis and coeliac disease: a study of relative prevalences. Gut 1998; 42:120–122.
50. Dickey W, McMillan SA, Callender ME. High prevalence of celiac sprue among patients with primary biliary cirrhosis. J Gastroenterol 1997; 25:328–329.
51. Bardella MT, Quatrini M, Zuin M, et al. Screening patients with celiac disease for primary biliary cirrhosis and vice versa. Am J Gastroenterol 1997; 92:1524–1526.
52. Fidler HM, Butler P, Burroughs AK, et al. Co-screening for primary biliary cirrhosis and coeliac disease. Primary biliary cirrhosis and coeliac disease: a study of relative prevalences. Gut 1998; 43:300.
53. Niveloni S, Dezi R, Pedreira S, et al. Gluten sensitivity in patients with primary biliary cirrhosis. Am J Gastroenterol 1998; 93:404–408.
54. Basso D, Gallo N, Guariso G, et al. Role of anti-transglutaminase (anti-tTG), anti-gliadin, and anti-endomysium serum antibodies in diagnosing celiac disease: a comparison of four different commercial kits for anti-tTG determination. J Clin Lab Anal 2001; 15:112–115.

Congestive Heart Failure:

Guidelines for the Primary Care Physician

Ira Galin, M.D.[1], and David A. Baran, M.D., F.A.C.C.[2]

Abstract

Heart failure is a common medical condition affecting nearly 5 million people each year in the United States, of whom 500,000 are newly diagnosed. The impact of this disease on society and the health care system is immense. Inpatient and outpatient costs are approximately $40 billion annually, almost $500 million of which is spent on heart failure medications alone. Beyond the problem of financial costs, however, it is imperative for us as health care professionals to improve our ability to prevent disease progression, decrease morbidity and mortality, and optimize patients' quality of life.

The use of a broad spectrum of treatments is reviewed in the context of a patient case study. Primary data justifying the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, digoxin, as well as beta blockers and spironolactone, is reviewed, with special reference to the stage of heart failure.

Key Words: Congestive heart failure, heart failure, treatment, guidelines, case study.

Background

HEART FAILURE (HF) is a common medical condition affecting nearly 5 million Americans each year in the United States, of whom 500,000 are newly diagnosed (1). The impact of this disease on society and the health care system is immense. Inpatient and outpatient costs are approximately $40 annually, almost $500 million of which is spent on heart failure medications alone (2). Beyond the problem of financial costs, however, it is imperative for us as health care professionals to improve our ability to prevent disease progression, decrease morbidity and mortality, and optimize patients' quality of life. The data and guidelines presented here are intended to assist in realizing these goals.

Heart failure affects 1.5 – 2.0% of the total US population, but the prevalence increases to 6 – 10% for Americans over the age of 65 (3 – 6). It is estimated that as many as 20 million people with clinically silent cardiac impairment will probably develop symptoms of HF in the next 1 – 5 years. Heart failure is the leading cause of hospitalization in the US, and approximately 80% of hospitalized patients with HF are over 65 years old (3 – 6).

The clinical syndrome of heart failure arises from the heart's inability to fill/relax and/or eject blood from the ventricle. The inability of the ventricle to fill with blood, due to a problem with ventricular relaxation, is referred to as diastolic dysfunction. This definition of diastolic dysfunction is based upon an elevated end-diastolic pressure in an otherwise normal ventricle. The inability of the ventricle to empty/eject blood is referred to as systolic dysfunction, typically defined as an ejection fraction ≤45%. Left ventricular dysfunction classically presents as pulmonary congestion (rales), an S3 gallop, dyspnea on exertion, shortness of

---

[1]Internal Medicine Resident and [2]Assistant Professor of Medicine, Transplant Cardiology, Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Some of the information was adapted from a Grand Rounds presentation to the Division of Cardiology, Mount Sinai School of Medicine, New York, NY on June 12, 2000 and updated July 2002.

Address all correspondence to David A. Baran, M.D., Zena and Michael A. Wiener Cardiovascular Institute, Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; Email: David.Baran@mountsinai.org

Dr. Baran has given six sponsored lectures in the past two years for Glaxo Smith Kline, which markets carvedilol. He received an honorarium for each lecture. The total received did not exceed the amount allowed by the policy of The Mount Sinai School of Medicine.

breath, paroxysmal nocturnal dyspnea, and/or orthopnea. It is important to note that the absence of rales does not rule out pulmonary venous congestion or left-sided HF, since patients with chronic HF can have specific adaptive compensatory mechanisms (7). If the right side of the heart is involved, patients may manifest signs and symptoms such as jugular venous distension, a pulsatile liver, and/or peripheral edema. A recent article evaluated the prognostic importance of elevated jugular venous pressure and a third heart sound in those patients with heart failure (8). The database was from the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial (9). In this analysis, elevated jugular venous pressure was associated with an increased risk of hospitalization for HF and death from HF. The presence of a third heart sound was associated with a similarly increased risk of the previously mentioned outcomes (9). There is a wide spectrum of disease that can cause ventricular dysfunction. While two-thirds of patients have HF from ischemic heart disease, others have identifiable causes such as hypertension, valvular disease, thyroid disease, alcohol use, myocarditis, sepsis, anemia, and nonischemic cardiomyopathy. A small percentage of people will have no identifiable cause for ventricular dysfunction (idiopathic dilated cardiomyopathy) (10). "Ventricular dysfunction" and "cardiomyopathy" refer only to the mechanism of dysfunction; the phrase "heart failure," as it will be used in this article, refers to the specific syndrome of signs and symptoms.

Symptomatic heart failure is described by functional limitation, using a New York Heart Association (NYHA) classification system. "NYHA class I" refers to patients who have no symptoms at any level of exertion. Normal physical activity does not cause them undue fatigue, or dyspnea, but such patients (as well as the patients in the other functional classes) have ventricular dysfunction. NYHA functional class II patients have symptoms with ordinary exertion, while class III patients have symptoms with less-than-ordinary exertion, and class IV patients have symptoms at rest. A simple rule to differentiate class II heart failure from class III heart failure is a "rule of 2's." In general, NYHA functional class II patients can walk two blocks and/or climb 2 flights of stairs without dyspnea, but class III or IV heart failure patients cannot. The system has several flaws: (a) inter-observer variability; (b) the inability to detect small changes in clinical status; and (c) the implicit assumption that all symptoms are secondary to heart failure.

Despite its flaws, the NYHA classification is important for choosing treatments, as well as predicting prognosis. A common misconception is that ejection fraction is the greatest predictor of outcome. For patients with a low NYHA class (such as class I), the ejection fraction may help estimate survival. However, at ejection fractions less than 25%, the predictive value diminishes. The NYHA classification is one of the best predictors of survival. Only 50% of patients remain alive 5 years after the diagnosis of heart failure, and those with severe symptoms (NYHA functional class III or IV) have a 1-year survival rate of only 40% (1, 2, 11).

Medical Therapies

This article will explore the rationale for therapies chosen for a patient with chronic heart failure. At times, we will touch upon important clinical "pearls" for managing these patients in an outpatient setting.

The treatment of heart failure begins with an extensive and complete evaluation of the patient. An initial visit should begin with a history and physical examination, to establish the etiology of ventricular dysfunction. One should inquire about a history of hypertension; diabetes; hyperlipidemia; coronary, valvular, or peripheral vascular disease; rheumatic fever; chest irradiation; exposure to cardiotoxic agents; and recent or current pregnancy. The practitioner should also inquire about the signs and symptoms of heart failure. Some baseline studies are important for guiding therapy and determining the etiology of ventricular dysfunction. These include, but are not limited to, the tests for levels of various constituents of blood and other body fluids, thyroid function tests, glycosylated hemoglobin if diabetic, lipid profile, liver function tests, complete blood count, and transferrin saturation and serum ferritin if considering hemochromatosis. In addition, initial evaluation should include an electrocardiogram (ECG) and a chest radiograph (although ECG and chest radiograph have low sensitivity and specificity in terms of determining the etiology of HF), and often, an echocardiogram.

In addition to the signs already mentioned, one should examine the patient for any jugular venous distension and/or a third heart sound, since their presence has been shown to have prognostic significance (9).

Therapy for heart failure begins by treating the underlying mechanism of ventricular dysfunction. One should also encourage coronary artery disease risk factor modification (treating lipid disorders and encouraging smoking cessation, regular exercise, weight loss, and limiting alcohol intake). Current American Heart Association guidelines (7) divide therapy according to the following criteria: high risk for heart failure (HF) but without structural heart disease or symptoms of HF (Stage A); structural heart disease but without symptoms of HF (Stage B); structural heart disease with prior or current symptoms of HF (stage C); and refractory HF requiring specialized interventions (Stage D). This article will primarily focus on the patient with symptomatic heart failure in the outpatient setting (Stage C) and will describe how to initiate and titrate medications for this general population. In addition, we will comment on the evidence regarding the indication or contraindication for use of commonly prescribed HF medications. The figure (12) is a helpful graphic synopsis of heart failure treatment, according to NYHA functional class. The components of this figure will be discussed at length below.

To best understand the outpatient management of heart failure and ischemic cardiomyopathy, we will examine several scenarios for a hypothetical patient, "J.K.," and assume that you are her primary care physician.

J.K. is a 62-year-old postmenopausal female with non-insulin-dependent diabetes, hypertension, and coronary artery disease (myocardial infarction 18 months ago, coronary artery bypass surgery also 18 months ago). She has a history of smoking 2 packs of cigarettes a day, but quit after her heart attack, and drinks a glass of red wine each night. Today, in your office, she has no complaints. She denies any signs or symptoms of heart failure. Her examination reveals blood pressure of 125/80 mm Hg, pulse of 78 per minute, and respiratory rate of 14 per minute. Her weight is 168 lbs and her height is 5'4". The examination reveals no jugular venous distension and no carotid bruits. Cardiopulmonary examination reveals a 2/6 holosystolic murmur that is most prominent at the apex and radiates to the axilla. There are no extra heart sounds and no rales. A well-healed sternotomy scar is noted; there is no hepatosplenomegaly or peripheral edema. Laboratory results show a normal set of chemistries (BUN and creatinine are 15 and 1.0 mg/dL respectively) except for an elevated serum glucose of 168 mg/dL. The complete blood count and coagulation studies are normal. A fasting serum lipid profile is as follows: total cholesterol 168 mg/dL, triglycerides 120 mg/dL, HDL 45 mg/dL, and LDL 98 mg/dL. An electrocardiogram reveals an old anterior wall myocardial infarction (MI). A recent echocardiogram shows a moderately dysfunctional left ventricle (ejection fraction of 35%), moderate mitral regurgitation, mild tricuspid regurgitation, and a mildly enlarged left atrium. No thrombus was noted in the left atrium or ventricle. Her medications include metformin 1000 mg twice a day, two 81 mg aspirin tablets each day, a hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitor (simvastatin 10 mg each day), atenolol 25 mg each day, and a low dose of an angiotensin-converting enzyme (ACE) inhibitor (lisinopril 10 mg each day). Which cardiac medication should this patient be taking for her left ventricular dysfunction?

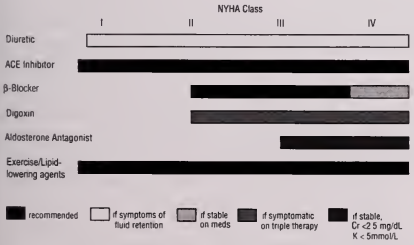

Figure. Recommended medication for heart failure patients. Adapted from Gomberg-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. Arch Intern Med 2001; 161(3):342–352 (12).

The patient illustrates a category of left ventricular dysfunction, after a myocardial infarction (non-acute setting), without symptoms of heart failure. In addition to a low-salt diet and daily exercise, her current medical regimen should be continued — but why?

There have been numerous studies looking at the use of ACE inhibitors in the setting of ventricular dysfunction and in the case of acute or recent MI. Before considering the clinical evidence for using ACE inhibitors, one should understand the physiologic rationale for using an ACE inhibitor. The renin-angiotensin-aldosterone system (RAAS) has evolved as an adaptive mechanism in the setting of hypovolemia. RAAS activation leads to salt and water retention. However, in the setting of heart failure, this compensatory mechanism is maladaptive. The kidneys perceive hypovolemia and hypoperfusion, and thus feed into a vicious cycle of increased RAAS activation and resulting increases in salt and water retention. This increased plasma volume results in more strain on the dysfunctional heart and a reduced cardiac output. In turn, there is worsening hypoperfusion of the kidneys and an increase in the degree of RAAS activation.

ACE inhibition inhibits (but does not completely stop) conversion of angiotensin I to angiotensin II. The effects of angiotensin II (via angiotensin II type 1 receptors) have been well studied (13 – 16); they include an increased load against which the left ventricle pumps (afterload), a stimulation of smooth muscle growth, and an increase in sodium and water retention. Angiotensin II also causes an increase in superoxide production, potentiates endothelin activity, causing vasoconstriction, and stimulates cardiac myocyte growth as well as interstitial and perivascular collagen synthesis, thus potentially contributing to ventricular remodeling and myocardial fibrosis. Therefore, ACE inhibition reduces ventricular remodeling and enlargement, and in this way acts to delay progression of left ventricular dysfunction.

There are several reasons why this patient should be taking an ACE inhibitor, assuming that there is: (a) no history of angioedema or anuric renal failure (secondary to an ACE inhibitor); (b) no pregnancy; (c) no increased creatine ≥3 mg/day; (d) no bilateral renal artery stenosis, or (e) potassium level > 5.5 mmol/L. Three trials have shown a decrease in all-cause mortality and in the risk of developing heart failure for patients with a recent MI, as a result of using ACE inhibitors, while other trials have shown beneficial effects on left ventricular remodeling, and delayed progression to HF in the same group of patients (17 – 21).

The Survival and Ventricular Enlargement (SAVE) trial randomized patients with a recent MI and a left ventricular ejection fraction of ≤40% to captopril (target of 150 mg/day) or placebo for an average of 42 months (22). The results showed that long-term therapy with captopril resulted in lower mortality and morbidity compared to placebo (20% vs. 25%, risk reduction = 29% [95% CI, 3 – 32, p=0.019] for overall reduction in mortality and reduction in risk of death from cardiovascular causes of 21% [95% CI, 20 – 50, p=0.014]). The result was seen for all patients, regardless of whether they received beta-blockers, aspirin, and/or thrombolytics.

The Acute Infarction Ramipril Efficacy (AIRE) (23) and the Acute Infarction Ramipril Efficacy Extension (AIREX) (24) trials showed similar reductions for patients with an acute MI and clinical or radiographic evidence of HF by randomizing patients to ramipril (goal of 5 mg/day) or placebo. The Trandolapril Cardiac Evaluation Study (TRACE) (19) was similar to the SAVE trial, but randomized patients with a recent MI and an ejection fraction of ≤35% to trandolapril (goal of 4 mg/day) or placebo. This trial showed similar reductions in the aforementioned endpoints. Also, other trials have shown the benefit of ACE inhibition after an MI, regardless of left ventricular function (16, 25, 26). There is one trial that fits our patient's profile, which is asymptomatic left ventricular dysfunction. The Studies of Left Ventricular Dysfunction (SOLVD)-prevention trial randomized patients with an ejection fraction ≤35% and a remote history of ischemic or nonischemic insult and with no (or minimal) symptoms of heart failure to enalapril (goal of 20 mg/day) or placebo (27). This trial showed a decrease in combined risk of death and hospitalization as well as decreased risk of hospitalization alone with enalapril. Although there was a trend toward a decrease in all-cause mortality, the results were not statistically significant (27).

Although there is clear evidence of the benefits of beta-blockers in the peri-myocardial infarction period and post-myocardial infarction periods, there is no evidence to support the use of beta-blockers for asymptomatic left ventricular dysfunction. The most recent evidence of the benefit of beta-blockers in the peri-/post-myocardial periods was seen in the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study (28). This trial investigated the long-term efficacy of carvedilol on morbidity and mortality in patients with left-ventricular dysfunction after acute MI, treated according to current evidence-based practice (28). Patients with proven acute MI and a left-ventricular ejection fraction of 40% or less were randomly assigned to carvedilol or placebo. Although there was no difference between the carvedilol and placebo groups in the number of patients with the primary endpoint, all-cause mortality alone was significantly lower in the carvedilol group than in the placebo group. The authors concluded that "in patients treated long-term after an acute myocardial infarction complicated by left-ventricular systolic dysfunction, carvedilol reduced the frequency of all-cause and cardiovascular mortality, and recurrent, non-fatal myocardial infarctions. These beneficial effects are additional to those of evidence-based treatments for acute myocardial infarction including ACE inhibitors."

Eight months later, the same patient returns to your office at one of her regularly scheduled follow-up visits. Today, she complains of some shortness of breath with her normal daily activities. She notes that she has had to sleep on 2 pillows instead of only one, and she can only walk 4 blocks before becoming short of breath, whereas she used to be able to walk 8 blocks. Her examination reveals blood pressure of 110/70, pulse of 75, and a respiratory rate of 18. Her weight today is 173 lbs. (+5 lbs). The remainder of her examination reveals jugular venous distension 5 cm above the right clavicle at 30 degrees and no carotid bruits. Cardiopulmonary examination reveals a 2/6 holosystolic murmur that is most prominent at the apex and radiates to the axilla. An S_3 is noted, and she has mild bibasilar rales. There is neither hepatosplenomegaly nor peripheral edema. Laboratory tests report serum BUN and creatinine levels of 35 and 1.4 mg/dL respectively, an elevated serum glucose of 148 mg/dL, a normal complete blood count, and normal coagulation studies. An ECG is unchanged from the previous visit. Her medication list is also unchanged (metformin 1000 mg twice a day, two 81 mg aspirin tablets each day, an HMG CoA reductase inhibitor (simvastatin 10 mg each day), atenolol 25 mg each day, and a low dose of an (ACE) inhibitor (lisinopril 10 mg each day).

Questions:

- What medications should this patient be taking?
- What medications should be stopped?
- Does this patient need to be hospitalized?
- Does this patient need a repeat echocardiogram?

At this visit, the patient describes symptoms of heart failure, with left ventricular dysfunction. It is important to establish the etiology of this progression. Is there a new heart attack or injury, or is this volume overload alone? We will assume that this patient is manifesting the natural progression of ischemic cardiomyopathy and is volume overloaded after eating salty foods.

Diuretics

There are several medications that this patient should continue to take, or begin to take, which have been shown to improve mortality, morbidity, or both. To begin with, diuretics are imperative. Each heart failure patient should know his or her optimal weight. This weight is based upon clinical trial and error and is optimal while the patient is clinically euvolemic and asymptomatic. Diuretics work by decreasing the reabsorption of sodium or chloride by the kidney. Loop diuretics, such as bumetanide, furosemide and torsemide are most commonly used and are the preferred agents. Other diuretics, such as thiazides, metolazone, and potassium-sparing diuretics may also be used alone or in conjunction with loop diuretics. Table 1 lists common loop diuretics used to treat HF, as well as the initial and maximum daily doses. Although there have been no long-term trials of diuretics (excluding spironolactone) and heart failure with regard to mortality and morbidity, these medications have become a cornerstone in the maintenance of volume status and symptom relief. Diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in intermediate-term trials (29–31). Trials evaluating the use of diuretics as monotherapy for heart failure have concluded that diuretics should not be used as monotherapy for HF, since they do not reduce mortality, unlike other therapeutic agents. While a patient is taking diuretics, it is important to maintain serum electrolyte values and to monitor renal function.

Angiotensin-Converting Enzyme Inhibitors

Once again, the use of ACE inhibitors is paramount. (The clinical rationale for the use of ACE inhibition was described above.) While there have been numerous trials evaluating the use of ACE inhibitors for NYHA classes I–IV, it is important to note that most trials excluded patients with a systolic blood pressure of 90 mm Hg or less, or impaired renal function

TABLE 1
Oral Loop Diuretics Commonly Used for Heart Failure

Medication	Initial Dose	Maximum Dose
bumetanide	0.5–1.0 mg once or twice daily	Titrate to achieve dry weight (up to 10 mg daily)
furosemide	20–40 mg once or twice daily	Titrate to achieve dry weight (up to 400 mg daily)
toresemide	10–20 mg once or twice daily	Titrate to achieve dry weight (up to 200 mg daily)

(serum creatinine greater than 2.5 mg/mL). Assuming that there is no contraindication to an ACE inhibitor (typically, systolic blood pressure less than 80 mm Hg, serum creatinine greater than 3 mg/mL, or a serum potassium greater than 5.5 mmol/L, angioedema, or pregnancy), a low dose should be initiated and increased slowly toward target levels (see Table 2). Not all ACE inhibitors are FDA-approved for heart failure. The ones that have been approved in the Unites States include enalapril, captopril, quinapril, lisinopril, fosinopril, and ramipril.

In the Vasodilator Heart Failure Trial-2 (V-HeFT-II) (32), patients with ischemic or nonischemic cardiomyopathy and mild-to-moderate heart failure (NYHA class II and III) were randomized to enalapril (up to 20 mg/day) or a combination of hydralazine (300 mg/day) plus isosorbide dinitrate (160 mg/day). V-HeFT-I had already shown that the combination of hydralazine and isosorbide dinitrate, in contrast to placebo, or prazosin (33), decreased mortality and increased left ventricular ejection fraction in patients with a left ventricular ejection fraction of less than 45% (NYHA class II and III), when it was associated with reduced exercise tolerance or cardiomegaly on chest radiograph. The results of V-HeFT-II showed a 28% reduction in mortality in the enalapril group compared to the hydralazine and nitrate combination group at 2 years, but lost statistical significance at 5-year follow-up. The reduction in mortality was mostly due to a reduction in the incidence of sudden cardiac death, while death that was due to pump failure was unchanged (32). The SOLVD Treatment study randomized patients with NYHA class II or III (ejection fraction of 35% or less) to enalapril or placebo (9). The enalapril group had an 11% reduction in mortality and a 30% reduction in hospitalizations for heart failure compared to placebo.

TABLE 2

ACE Inhibitors Commonly Used for Heart Failure

Medication	Initial Dose	Maximum Dose
captopril	6.25 mg 3 times daily	50 mg 3 times daily
enalapril	2.5 mg twice daily	10 – 20 mg twice daily
fosinopril	5 – 10 mg once daily	40 mg once daily
lisinopril	2.5 – 5 mg once daily	20 – 40 mg once daily
quinapril	10 mg twice daily	40 mg twice daily
ramipril	1.25 – 2.5 mg once daily	10 mg once daily

Enalapril was also studied in NYHA class IV patients in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (33). Patients with NYHA functional class IV heart failure were randomized to placebo or enalapril (up to 40 mg each day). This trial was stopped prematurely because there was a 27% reduction in all-cause mortality at 6 months and 31% reduction at 12 months. Improvement in NYHA class was observed in 42% of patients in the enalapril group compared to only 22% of the placebo group. However, there was no effect on the combined risk of death and hospitalization for heart failure (34). Captopril was evaluated in the Captopril-Digoxin Multicenter Trial (35). Study patients were mostly NYHA class II, already taking a diuretic, and they were randomized to digoxin, captopril, or placebo. The captopril group had decreased emergency care visits, as well as fewer hospitalizations for worsening heart failure compared to placebo (34, 35).

Recommendations for Patient J.K.

In contrast to the above medical regimen, there are some medications that should not be used by acute or chronic heart failure patients, if possible. These medications include nonsteroidal anti-inflammatory drugs, most antiarrhythmics, thiazinediones, and metformin. Moreover, in acute decompensated heart failure, one must exercise caution when using beta-blockers. Beta-blockers should never be initiated in the setting of acute decompensated HF. In addition, if a patient is currently taking a beta-blocker and presents with an acute exacerbation, with evidence of hypoperfusion and low cardiac output, then consideration should be given to reducing the dose of beta-blocker or temporarily stopping it. For our patient, we could consider stopping the atenolol, since it is a low-dose beta-blocker.

This patient does not necessarily need to be hospitalized, since she is known to you (the primary care provider). Prescribing medications to provide symptomatic relief as well as to retard progression of HF can be done on an outpatient basis. If this patient were not known from prior visits, it would be best to send her for an inpatient evaluation to determine ischemic causes of heart failure, as well as to rule out other causes of left ventricular dysfunction.

Additional questions to ask are: "What dose of ACE inhibitor should one use to treat heart failure? Does one get the same effect if the patient cannot tolerate the dose used in clinical trials?"

Dosing of ACE Inhibitors

Two trials have addressed these questions (36, 37). Regardless of the high doses used in the large, randomized clinical trials, the NETWORK study showed that there was no difference in benefit between enalapril 2.5 mg bid, 5 mg bid, or 10 mg bid in patients with NYHA class II–IV (36). The study looked at a primary combined endpoint (death, HF-related hospitalizations, and progression of HF), as well as several individual secondary endpoints (death, HF-related hospitalizations, and progression of HF) and found no statistically significant correlation between doses and outcomes. The Accupril Congestive Heart Failure Investigation and Economic Variable Evaluation (ACHIEVE) trial is currently evaluating the effects of different doses of quinapril on mortality (38). Finally, the Assessment of Treatment with Lisinopril and Survival (ATLAS) looked at the differences between high-dose and low-dose lisinopril (37). The results of this trial showed no difference in mortality for patients with class II through IV heart failure. However, there were fewer hospitalizations (p=0.002) for all causes and HF hospitalization in the high-dose group. Although one would like to achieve the high doses used in the large, randomized clinical trials, one must also try to minimize potential side effects. These include hypotension, worsening renal function, potassium retention, cough, and angioedema. Yet, while lower doses may minimize some of these side effects, it is important to realize that lower doses may produce smaller differences in outcome. In patient J.K.'s case the blood pressure is not low, and attempts should be made, at successive visits, to increase ACE inhibitor dosage.

What if this same patient developed a cough, and could not tolerate an ACE inhibitor? Is there any evidence that an angiotensin II receptor blocker (ARB) has equivalent or superior effects in the same group of patients?

Angiotensin Receptor Blockers

This clinical question has been addressed in several clinical trials. The first direct comparison of an angiotensin II receptor blocker (ARB) to an ACE inhibitor was the Evaluation of Losartan in the Elderly (ELITE) study (39). This trial randomized elderly patients with NYHA class II–IV heart failure, who had never been treated with an ACE inhibitor, to either losartan or captopril for 48 weeks. This trial was designed to compare the safety profile of ACE inhibitors and ARBs in the treatment of HF. Unexpectedly, there was a trend to decreased mortality in the ARB group (4.8% vs. 8.7%), a risk reduction of 46% (p=0.035) (39). The lower mortality rate resulted mainly from a reduction in sudden cardiac death. Also, losartan was shown to be better tolerated than captopril (37). These results led to ELITE II (40), which was designed to confirm the survival advantage seen in ELITE. However, this trial failed to demonstrate any survival benefit in the losartan group compared to placebo. Ironically, it showed a trend toward an increase in mortality in the losartan group compared to the captopril group, especially in regard to sudden cardiac death. Losartan was again shown to be better tolerated than the ACE inhibitor.

ACE inhibitors have clearly been shown to reduce mortality and morbidity across all classes of heart failure as well as for asymptomatic left ventricular dysfunction. In addition, ARBs have not been shown to be either superior, or equivalent, in the treatment of heart failure compared to ACE inhibitors. Thus, one must use these ARBs with caution and mainly for those patients who cannot tolerate an ACE inhibitor.

However, does a combination of the two (ACE inhibition and angiotensin II receptor blockade) have an equivalent or superior effect?

Combination Therapy with ACE Inhibitors and ARBs

The rationale for this approach is based on the pharmacology of ACE inhibitors. The blockade of ACE inhibitors is not complete, since there is some "escape" of angiotensin I, which is converted to angiotensin II. Thus, it is believed that blocking the renin-angiotensin cascade in multiple spots will improve overall patient outcomes. One of the first studies to look at this was the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial (41). This trial compared candesartan, enalapril, and combination candesartan plus enalapril for patients with NYHA class II–IV heart failure, an ejection fraction of less than 40%, and a 6-minute walk distance of less than 500 meters. Although there was no difference in 6-minute walk, ejection fraction, ventricular volumes, neurohormonal levels, quality of life, or NYHA functional class, there was a nonsignificant increase in ejection fraction in the combination group. Also, there was no significant difference in death, hospitalization for HF, or any hospitalizations, but there was a nonsignificant difference in mortality between the combination, candesartan, and enalapril groups (8.7%, 6.1%, and 3.7% respectively) (41).

The Valsartan Heart Failure Trial (Val-HeFT) was the next trial to compare ARBs, ACE inhibitors, and combination therapy (42). Patients with NYHA classes II–IV heart failure were randomized to valsartan or placebo. In this trial some patients were on ACE inhibitors (92.6% valsartan vs. 92.8% placebo) and/or beta-blockers (34.5% in the valsartan group on beta-blockers vs. 35.3% placebo). This study showed the overall mortality rate between treatment groups to be similar, while the combined endpoint of mortality and morbidity was significantly lower in the valsartan group (28.8% vs. 32.1%; p=0.009). The combined endpoint was defined as cardiac arrest with resuscitation, hospitalization for HF, or administration of intravenous inotropic or vasodilator drugs for four hours or more with or without hospitalization. There was also a significant improvement in the secondary endpoints (NYHA class, ejection fraction, signs and symptoms of HF, and quality of life) in the valsartan group compared to placebo (p<0.01) (42).

The benefits of valsartan were not seen in the heterogenous black study population, and there was a worrisome trend toward increased mortality with valsartan in this group. A post hoc analysis divided the study population into four groups, based upon whether or not the patient was on an ACE inhibitor and/or a beta-blocker. For those patients receiving both an ACE inhibitor and a beta-blocker, the addition of valsartan had an adverse effect on mortality and a trend toward an increase in combined mortality and morbidity. For patients who were receiving neither an ACE inhibitor nor a beta-blocker, there was a significantly lower mortality rate in the valsartan group than the placebo group (42). One can conclude from this trial that if a patient is receiving neither an ACE inhibitor nor a beta-blocker, valsartan will decrease the likelihood of mortality with a probability of decreased combined mortality and morbidity. However, for patients on both a beta-blocker and an ACE inhibitor, the addition of valsartan will have an adverse effect on the combined endpoint and on mortality. The Candesartan in Heart failure — Assessment of Reduction in Mortality and morbidity (CHARM) trial — is currently evaluating candesartan in heart failure, and will contain one arm that will treat patients with a combination of candesartan and an ACE inhibitor (43).

The side effects of ARBs are similar to those seen with ACE inhibitors. However, since angioedema and cough are bradykinin mediated, these two side effects generally do not occur in patients treated with ARBs.

Assuming that this patient can tolerate an ACE inhibitor and that she is stable on her current regimen, but still complains of shortness of breath with daily activities, are there any other medications from which this patient would benefit? (Also, assume that the patient does not have any signs or symptoms of acutely decompensated heart failure.)

Digoxin

Another medication frequently mentioned in the treatment of heart failure is digoxin. This medication is traditionally considered as a positive inotrope via cardiac sodium/potassium adenosine triphosphatase (ATPase) pump inhibition. However, digoxin is also a neurohumoral modulator, causing a decrease in sympathetic tone and an increased vagal/parasympathetic tone. Other trials of positive inotropes have uniformly shown excess cardiac mortality, but digoxin has no excess mortality effect (possibly due to its weak inotropic effect). The Digitalis Investigation Study group (DIG trial) examined NYHA class II–IV HF patients who had not received digoxin and randomized them to either digoxin or placebo (44). While there was no difference in mortality, arrhythmias, or occurrence of myocardial ischemia, the digoxin group did have a lower rate of overall hospitalization and hospitalization due to HF (44).

Withdrawal of Digoxin

The flip-side of this equation is the patien with HF who is withdrawn from digoxin therapy. Both the Prospective Randomized Study o Ventricular Function and Efficacy of Digoxi (PROVED) (45) and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) (46) showe detrimental effects of withdrawing digoxin in stable heart failure patient. The patients in RA

DIANCE were already on diuretics and an ACE inhibitor in addition to digoxin. The withdrawal of digoxin for three months led to clinically significant worsening of HF as assessed by NYHA class, patient's subjective assessment, left ventricular ejection fraction and left ventricular end diastolic dimension, compared to those who continued digoxin (46). PROVED showed similar results (45).

If digoxin does not improve mortality, then why use it at all for patients with a normal sinus rhythm?

In the current recommendations for heart failure management, digoxin should be added to achieve improvement in clinical status for those patients with HF who are already treated with diuretics, ACE inhibitors, and a beta-blocker. Withdrawal of digoxin may do more potential harm than the benefits seen after starting the medication for heart failure therapy.

Side effects of digoxin include cardiac arrhythmias (ectopic and re-entrant rhythms and heart block), gastrointestinal symptoms (anorexia, nausea, and vomiting), and neurologic complaints (visual disturbances, disorientation, and confusion). The potential side effects are more commonly associated with elevated serum concentrations. However, these effects may manifest at lower serum levels in the setting of hypokalemia, hypomagnesemia, or hypothyroidism.

The same patient returns to your office and is now euvolemic by weight and by examination. Her BUN and creatinine values are now 15 and 1.1 mg/dL respectively. Her potassium is normal, her blood pressure is 120/80 mm Hg, and her pulse beats 72 per minute. Are there any additional medications from which this patient would benefit? Her current regimen includes: an oral anti-hypoglycemic agent (glipizide 10 mg each day), two 81 mg aspirin tablets each day, furosemide 80 mg po qd, an HMG CoA reductase inhibitor (simvastatin 10 mg each day), digoxin 0.125 qd, and a low dose (lisinopril 10 mg each day) of an ACE inhibitor. The atenolol had been stopped when the patient presented with an acute exacerbation of heart failure, and was never restarted.

Beta-Blockers

Initially beta-blockers were thought to be detrimental to HF patients. However, one of the hallmarks of severe heart failure is activation of the sympathetic nervous system, and high serum catecholamine levels. Beta-blockers inhibit these effects. Strong evidence (discussed below) supports the role of beta-blockers for HF patients, with resultant improvement in morbidity, mortality, and delay of HF progression.

Another misconception about treating heart failure is that the beneficial effects of beta-blockers are a "class-effect." While there are certain classes of medications that have the same effect on a certain illness or produce the same side effects, this is not true for beta-blockers and heart failure. Beta-blockers from three classes, β1-selective, β1-β2 nonselective, and β-nonselective + α-blockade, have been studied in the setting of heart failure. The four drugs studied have been metoprolol, bisoprolol, bucindolol, and carvedilol.

Two trials have looked at the utility of the β1-selective agent metoprolol. The Metoprolol in Dilated Cardiomyopathy (MDC) trial (47) randomized patients with NYHA functional classes II–IV (who were already taking digitalis, diuretics, nitrates, and/or ACE inhibitors designed to achieve optimal compensation of their heart failure). Diabetics, patients with significant coronary artery disease, and patients with other serious illnesses (including chronic obstructive pulmonary disease) were excluded from this trial. The investigators found that those treated with metoprolol did not have a significant decrease in mortality, but had significantly lower need for heart transplantation, and had improved left ventricular ejection fraction, exercise capacity, and NYHA functional class, compared to placebo at an 18-month follow-up.

As the results of the MDC trial were promising, it led to the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study (48, 49). Nearly 4,000 patients with NYHA classes II–IV were randomized to a sustained-release preparation of metoprolol or placebo. This trial was stopped early because of the favorable results in the sustained-release metoprolol-treated group. MERIT-HF demonstrated decreased mortality with metoprolol (specifically resulting from sudden cardiac death or pump failure) regardless of ischemic or nonischemic etiology. This difference was seen across most demographic groups. The metoprolol group also had a reduced requirement for hospitalization, improved NYHA functional class, and improved patient-assessed well-being.

The U.S. Carvedilol Heart Failure Program, consisting of 4 coordinated studies (50–53) of patients with NYHA class II, III, or IV who had an ejection fraction of less than 35%, and the

Australia and New Zealand Heart Failure Research Collaborative Group (54), consisting of one trial of patients with NYHA class I, II, or III and an ejection fraction of less than 45%, have shown the efficacy of carvedilol in HF patients. The Australia/New Zealand group showed that for patients with heart failure secondary to ischemic cardiomyopathy, at 6 months the carvedilol group had improved left ventricular function, but slightly worsened symptoms compared to the placebo group (54). At 12 months, the carvedilol group still had an improvement in left ventricular function and a decrease in the combined endpoint of death or hospitalization. However, there was no effect on mortality, exercise performance, symptoms, or episodes of worsening heart failure.

The U.S. Carvedilol Heart Failure Study (50) showed that carvedilol reduces the risk of death and risk of hospitalization for cardiovascular causes in patients with HF who are receiving treatment with digoxin, diuretics, and an ACE inhibitor. Overall mortality was 7.8% in the placebo group compared to 3.2% in the carvedilol group ($p<0.001$) (50). Death from progressive heart failure was 3.3% in the placebo group and 0.7% in the carvedilol group (50).

The Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) study (51) showed that in those subjects with mild-to-moderate HF due to systolic dysfunction, treatment with carvedilol resulted in dose-dependent improvement in left ventricular function and reduction in mortality and hospitalization rates (51). The US Carvedilol Heart Failure Study (52) showed that for patients with mildly symptomatic stable HF due to systolic dysfunction, carvedilol reduced clinical progression of heart failure and mortality. There was no difference in quality of life scores and the distance walked in a 9-minute treadmill test between the carvedilol group and a placebo group. The mortality rate for the placebo group was 4% vs. 0.9% in the carvedilol group (95% CI 0.045 to 1.174, $p=0.048$) (52). Finally, the Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (PRECISE) trial (53) showed that while there was no statistically significant difference in hospitalization for cardiovascular etiology or death, there was a statistically significant difference in combined death and cardiovascular hospitalization. The authors concluded that for patients who tolerate drug treatment and are being treated with diuretics, ACE inhibitors and digoxin for moderate-to-severe stable heart failure due to systolic dysfunction, the addition of carvedilol decreased death or cardiovascular hospitalization (53).

The collaborative US Carvedilol Heart Failure Program was terminated early as a result of a reduction in mortality among patients treated with carvedilol. According to intention-to-treat analysis, overall mortality risk was reduced significantly (by 65%) in the carvedilol group as compared to the placebo group (3.2% vs. 7.8%). Mortality was significantly lower in patients with NYHA class II symptoms (1.9% vs. 5.9%) and 65% lower among those with NYHA III symptoms (4.2% vs. 11%). One of the criticisms is that a reduction in mortality includes data from some trials in which the primary endpoints were not achieved (55, 56).

Most recently the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS) (57) evaluated the safety and efficacy of carvedilol in NYHA class IV patients. When the results showed a 35% reduction in death in the carvedilol group compared to the group with placebo, and the trial was stopped early. Patients were excluded from this study if uncorrected primary valve disease or a form of reversible cardiomyopathy caused the heart failure; if they were likely to receive cardiac transplantation; if they had severe primary pulmonary, renal, or hepatic disease; or if they had a contraindication to beta-blocker therapy. Patients who received intensive care, had marked fluid retention, or were receiving intravenous vasodilator or intravenous positive inotropic agents were not enrolled. Such patients may not have a favorable response to carvedilol.

Currently, the Carvedilol or Metoprolol European Trial (COMET) (58) is comparing the use of carvedilol and metoprolol for heart failure. This trial represents the first direct, randomized comparison of these two FDA-approved beta-blockers for the treatment of HF. The trial is ongoing, with results expected in the next 1 – 2 years.

Nonselective beta-blockers have also been studied in large, randomized trials. Bisoprolol was studied in two trials, and a third is currently planned. The Cardiac Insufficiency Bisoprolol Study (CIBIS-I) (59) was a placebo-controlled trial of bisoprolol for patients with symptomatic ischemic or nonischemic cardiomyopathy, who had NYHA function class III or IV, were treated with diuretics and vasodilators, and had an ejection fraction of less than 40%. A 20% reduction in mortality was observed, but this did not reach statistical significance due to insufficient patient numbers (the trial was underpowered). The observed benefit was limited to those with nonischemic cardiomyopathy. An improvement in functional status and a decrease in hospitalization for cardiac decompensation was observed in the bisoprolol group (59). These promising results prompted the CIBIS-II study (60), which was stopped early (after 18 months) because of a 32% reduction ($p<0.001$) in all-cause mortality in the bisoprolol-treated group. The CIBIS-II trial showed that bisoprolol was well tolerated and reduced mortality and hospitalization rates for patients with stable HF (60). The results of this trial are impressive, and the trial itself constitutes a landmark in the development in beta-blockade as a treatment for heart failure (56).

The Beta-blocker Evaluation of Survival Trial (BEST) (61) evaluated bucindolol for patients with advanced heart failure. This trial also enrolled a large subset of patients who were either women or minorities. A total of 2,708 patients, mostly of class III (92%) heart failure and some of class IV (8%), who were already optimized on a heart failure regimen but not taking a beta-blocker, were randomized to bucindolol or placebo. The trial was terminated after the seventh interim analysis showed no mortality difference between the two groups. The results of this trial are based on a completed follow-up of 2 years. The BEST study concluded that there was no significant improvement in overall survival for patients in the bucindolol group (61). The authors hypothesized that the lack of significant reduction in overall mortality was secondary to a different patient population, since there was a significant decrease in mortality in a subgroup of non-black patients. There was actually an increase in mortality in the black population in the BEST study, in contrast to the metoprolol or carvedilol studies, where this was not observed. It is possible that different racial groups may have different pharmacological responses to beta-blockers (61).

It is important to emphasize that the addition of beta-blockers is appropriate only for the regimen of the euvolemic, stabilized heart failure patient. The potential side effects of beta-blockers include fluid retention and worsening HF, fatigue, depression, bradycardia and heart block, hypotension, and bronchospasm (in those prone to, or diagnosed with, bronchospastic diseases). In an outpatient setting these medications can be safely titrated every 2–4 weeks. The initial and goal doses are listed in Table 3.

One last point concerning this patient is that, since she has a systolic blood pressure of 120 mm Hg, the ACE inhibitor should be up-titrated, perhaps alternating with up-titration of the beta-blocker. Since atenolol has not been shown to be of benefit for HF, the patient should be placed on carvedilol or metoprolol sustained release.

The same patient returns for her follow-up visits over the next several years and does well, but her heart failure progresses. She now complains of dyspnea at rest, but has no finding of acute or decompensated heart failure (rales, orthopnea, paroxysmal nocturnal dyspnea, elevated jugular venous pulse, increased lower extremity edema, or worsened dyspnea on excretion). Her medication regimen includes an oral glucose-control agent (not metformin), two 81 mg aspirin tablets each day, an HMG CoA reductase inhibitor, carvedilol 25 po bid, furosemide 100 mg po bid, and a moderate dose (lisinopril 40 mg each day) of an ACE inhibitor regimen. Are there any additional medications that might help this patient in regard to mortality, morbidity, or both? You remember reading something about aldosterone antagonism and HF, but cannot remember if this patient fits into the patient profile of the spironolactone trial. Is there a role for an aldosterone antagonist in the setting of heart failure? If so, for which patients?

To begin with, this patient has NYHA functional class IV heart failure. It is important now to refer this patient to a specialist, ideally to a cardiologist who specializes in the management of heart failure. Following is a review of additional therapies that can affect (positively or negatively) mortality and/or morbidity.

Spironolactone

The Randomized Aldactone Evaluation Study (RALES) trial (62) examined the use of

TABLE 3

Beta-Blockers Commonly Used for Heart Failure

Medication	Initial Dose	Maximum Dose
bisoprolol	1.25 once daily	10 mg once daily
carvedilol	3.125 mg twice daily	25 mg twice daily; 50 mg twice daily for patients more than 85 kg
metoprolol CR/XL	12.5–25 mg daily	200 mg once daily

aldactone in a select group of patients (63, 64). HF patients in NYHA functional class III or IV (and with a diagnosis of heart failure at least 6 weeks before enrollment), who received an ACE inhibitor and a loop diuretic, and had an ejection fraction of less than 35% within 6 weeks of enrollment were randomized to spironolactone (25 mg orally each day) or placebo. Some of the exclusion criteria included a serum creatinine level of greater than 2.5 mg/dL or a serum potassium level greater than 5.0 mmol/L. The trial was stopped early, due to a significant 31% decrease in cardiac death (specifically, progression of heart failure and sudden death) observed in the spironolactone (25 mg orally each day) group. Spironolactone patients also had decreased hospitalization for all cardiac causes, mostly due to a decrease in HF hospitalizations (64). Given decreases in sudden death, it is possible that an increase in serum potassium in the spironolactone group was at least partially responsible.

For this patient, if there are no contraindications to the medication and her serum creatinine and potassium levels are less than 2.5 mg/dL and 5.0 mmol/L respectively, then spironolactone should be added to the regimen. The recent ACC/AHA consensus HF guidelines suggest that spironolactone may be of benefit for a select group of patients (7). The addition of low doses of spironolactone (25 mg each day) should be considered for patients with recent or current symptoms at rest despite the use of digoxin, diuretics, ACE inhibitor, and a beta-blocker. Patients should also have levels of serum creatinine and potassium of less than 2.5 mg/dL and 5.0 mmol/L respectively, before therapy is initiated.

Calcium-Channel Blockers

Calcium-channel blockers have been studied in several large trials. The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial (65) documented the safety of amlodipine for HF. In fact, this is the first calcium-channel blocker that was NOT associated with an increased mortality and morbidity among patients with severe heart failure. Amlodipine lowered mortality in a subgroup of patients with nonischemic cardiomyopathy. PRAISE-2 (enrolling only patients with nonischemic cardiomyopathy) failed to confirm these results, but at least it did not demonstrate increased mortality with this agent (66).

Other trials such as V-HeFT III (67) and Diltiazem in Dilated Cardiomyopathy (DiDi) (68), also failed to show any benefit for HF patients treated with a calcium-channel blocker (felodipine and diltiazem respectively). While calcium-channel blockers do not have any beneficial effects for heart failure patients, if their use is indicated (angina or refractory hypertension), then only one shown to be safe should be employed (preferentially amlodipine).

Oral Phosphodiesterase III Inhibitors

Intravenous phosphodiesterase III inhibitors are used in acute, mostly inpatient, decompensated heart failure situations. There has been one trial, the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial (69), which compared oral milrinone to placebo for patients treated with digoxin, diuretics, and ACE inhibitors. Long-term therapy with oral milrinone increased the mortality and morbidity of treated patients with severe heart failure.

Exercise

Patients were once told that bedrest was an adjunct to medical therapy. Although this may be the case for an unstable patient, moderate exercise training for patients with heart failure has been shown to improve functional capacity, quality of life, and improved outcome compared to those without training (70).

Conclusions

Our understanding of heart failure continues to improve as new therapies are subjected to the rigors of multicenter trials. In this paper, we have attempted to cover numerous trials in the context of a typical patient presentation. One of the most important points to remember is that heart failure is a progressive, relentless, and eventually fatal illness. At each stage of the disease, the practitioner may have the opportunity to prescribe medications that will extend the longevity of the patient and/or at least improve the patient's quality of life. Therapies such as beta-blockade and ACE inhibition have been shown to reduce disease progression. A specific combination of medications discussed in this paper, applied to each individual heart failure patient, will help prolong life and reduce suffering. In addition, knowledge of the underlying evidence supporting the use of these agents will help the practitioner customize a medica regimen, selecting from the variety of medications available.

References

1. American Heart Association 1998 Heart and Stroke Statistical Update. Dallas (TX): American Heart Association; 1998.
2. O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: time for a different approach. J Heart Lung Transplant 1994; 13(4):S107–S112.
3. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J 1997; 133(6):703–712.
4. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993; 22(4 Suppl A):6A–13A.
5. Kannel WB, Belanger AJ. Epidemiology of heart failure. Am Heart J 1991; 121(3 Pt 1):951–957.
6. Kannel WB. Epidemiology and prevention of cardiac failure: Framingham Study insights. Eur Heart J 1987; 8 Suppl F:23–26.
7. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001; 38(7):2101–2113.
8. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med 2001; 345(8):574–581.
9. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991; 325(5):293–302.
10. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. N Engl J Med 1994; 331(23):1564–1575.
11. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000; 342(15):1077–1084.
12. Gomberg-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. Arch Intern Med 2001; 161(3):342–352.
13. Baruch L, Anand I, Cohen IS, et al. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. Vasodilator Heart Failure Trial (V-HeFT) Study Group. Circulation 1999; 99(20):2658–2664.
14. Su J, Barbe F, Houel R, et al. Comparison between angiotensin receptor antagonism and converting enzyme inhibition in heart failure. Differential acute effects according to the renin-angiotensin system activation. Basic Res Cardiol 1999; 94(2):128–135.
15. Cohn JN. Heart failure: future treatment approaches. Am J Hypertens 2000; 13(5 Pt 2):74S–78S.
16. Blaufarb IS, Sonnenblick EH. The renin-angiotensin system in left ventricular remodeling. Am J Cardiol 1996; 77(13):8C–16C.
17. Pfeffer MA, Greaves SC, Arnold JM, et al. Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. Circulation 1997; 95(12):2643–2651.
18. Tavazzi L, Volpi A. Remarks about postinfarction prognosis in light of the experience with the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico (GISSI) trials. Circulation 1997; 95(5):1341–1345.
19. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995; 333(25):1670–1676.
20. Kingma JH, van Gilst WH, Peels CH, et al. Acute intervention with captopril during thrombolysis in patients with first anterior myocardial infarction. Results from the Captopril and Thrombolysis Study (CATS). Eur Heart J 1994; 15(7):898–907.
21. van Gilst WH, Kingma JH, Peels KH, et al. Which patient benefits from early angiotensin-converting enzyme inhibition after myocardial infarction? Results of one-year serial echocardiographic follow-up from the Captopril and Thrombolysis Study (CATS). J Am Coll Cardiol 1996; 28(1):114–121.
22. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327(10):669–677.
23. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993; 342(8875):821–828.
24. Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. Lancet 1997; 349(9064):1493–1497.
25. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet 1995; 345(8951):669–685.
26. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med 1995; 332(2):80–85.
27. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992; 327(10):685–691.
28. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001; 357(9266):1385–1390.
29. Brater DC. Diuretic therapy. N Engl J Med 1998; 339(6):387–395.
30. Cody RJ, Kubo SH, Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. Arch Intern Med 1994; 154(17):1905–1914.
31. Wilson JR, Reichek N, Dunkman WB, Goldberg S. Effect of diuresis on the performance of the failing left ventricle in man. Am J Med 1981; 70(2):234–239.
32. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991; 325(5):303–310.
33. Cohn JN, Johnson G. Heart failure with normal ejection fraction. The V-HeFT Study. Veterans Administration Cooperative Study Group. Circulation 1990; 81(2 Suppl):III48–III53.
34. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987; 316(23):1429–1435.
35. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. The Captopril-Digoxin Multicenter Research Group. JAMA 1988; 259(4):539–544.

36. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. The NETWORK Investigators. Eur Heart J 1998; 19(3):481–489.

37. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999; 100(23):2312–2318.

38. Davidson NC, Coutie WJ, Webb DJ, Struthers AD. Hormonal and renal differences between low dose and high dose angiotensin converting enzyme inhibitor treatment in patients with chronic heart failure. Heart 1996; 75(6):576–581.

39. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997; 349(9054):747–752.

40. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial — the Losartan Heart Failure Survival Study ELITE II. Lancet 2000; 355(9215):1582–1587.

41. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation 1999; 100(10):1056–1064.

42. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001; 345(23):1667–1675.

43. Swedberg K, Pfeffer M, Granger C, et al. Candesartan in heart failure — assessment of reduction in mortality and morbidity (CHARM): rationale and design. Charm-Programme Investigators. J Card Fail 1999; 5(3):276–282.

44. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 1997; 336(8):525–533.

45. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol 1993; 22(4):955–962.

46. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993; 329(1):1–7.

47. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet 1993; 342(8885):1441–1446.

48. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353(9169):2001–2007.

49. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000; 283(10):1295–1302.

50. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334(21):1349–1355.

51. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 1996; 94(11):2807–2816.

52. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. Circulation 1996; 94(11):2800–2806.

53. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation 1996; 94(11):2793–2799.

54. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. Lancet 1997; 349(9049):375–380.

55. Frishman WH. Carvedilol. N Engl J Med 1998; 339(24):1759–1765.

56. Bristow MR. beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101(5):558–569.

57. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344(22):1651–1658.

58. Poole-Wilson PA, Cleland JG, Di Lenarda A, et al. Rationale and design of the carvedilol or metoprolol European trial in patients with chronic heart failure: COMET. Eur J Heart Fail 2002; 4(3):321–329.

59. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation 1994; 90(4):1765–1773.

60. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353(9146):9–13.

61. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001; 344(22):1659–1667.

62. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709–717.

63. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999; 341(8):577–585.

64. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001; 345(23):1689–1697.

65. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med 1996; 335(15):1107–1114.

66. Thackray S, Witte K, Clark AL, Cleland JG. Clinical trials update: OPTIME-CHF, PRAISE-2, ALL-HAT. Eur J Heart Fail 2000; 2:209–212.

67. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Circulation 1997; 96(3):856–863.

68. Figulla HR, Gietzen F, Zeymer U, et al. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy. Results of the Diltiazem in Dilated Cardiomyopathy Trial. Circulation 1996; 94(3):346–352.

69. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991; 325(21):1468–14675.

70. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999; 99(9):1173–1182.

A Rare Cause of Pituitary Stalk Enlargement and Panhypopituitarism

Shehzad Basaria, M.D.[1], Julie S. Krop, M.D.[1], and Milena Braga-Basaria, M.D.[2]

Abstract

Pituitary stalk involvement is seen in a variety of medical conditions such as infectious diseases, infiltrative diseases and tumors (intracranial and metastatic). Metastatic cancer has a greater propensity to involve the infundibulum and neurohypophysis. We report a case of a 68-year-old man who presented with thickening of the stalk, panhypopituitarism, diabetes insipidus and generalized lymphadenopathy. Lymphoma was diagnosed on axillary lymph node biopsy and lymphomatous involvement of the infundibulum was suspected. Although infundibular thickening resolved and diabetes insipidus improved after chemotherapy, panhypopituitarism persisted.

Key Words: Panhypopituitarism, lymphoma.

Introduction

THE PITUITARY GLAND AND INFUNDIBULUM can be involved in a variety of medical conditions, such as infiltrative diseases (hemochromatosis, sarcoidosis, Wilson's disease), infections (tuberculosis, fungal infections) and tumors (intracranial and metastatic) (1, 2). Metastatic cancers have a predisposition to spread to the posterior pituitary and the infundibulum, with diabetes insipidus (DI) being a common pathology at presentation. Lymphomas are known to metastasize to the pituitary gland (2). Infundibular thickening is the most common finding on the magnetic resonance imaging (MRI) in these patients. We report a middle-aged man who presented with DI, pituitary stalk thickening and generalized lymphadenopathy. Axillary lymph node biopsy showed high-grade B-cell lymphoma. Lymphadenopathy and infundibular thickening resolved after chemotherapy, and DI improved. However, anterior pituitary function did not improve.

Case Report

A 68-year-old man was admitted with a 6-week history of polyuria, polydipsia, postprandial nausea and emesis The patient had been well until 6 months previously, when he developed anorexia and early satiety. He lost 20 lbs over this period of time. He denied any abdominal pain, but six weeks before admission he developed emesis, which occurred 60 – 90 minutes after a meal. He denied any dysphagia, odynophagia, fever, night sweats, headaches, head trauma, or visual symptoms. He was not taking any medications. He did complain of polyuria (6 – 8 times, both diurnal and nocturnal) and polydipsia, decreased libido, impotence and muscle weakness. There was no history of hyperpigmentation. His medical history and family history were unremarkable.

On physical examination, a 3.5 cm left axillary lymph node was palpable. There was no cervical lymphadenopathy. The visual fields were normal and there was no organomegaly. Both testes were atrophic. Neurological exami-

---

[1] Division of Endocrinology and Metabolism, Johns Hopkins University School of Medicine, Bayview Medical Center, and [2]SEMPR — Serviço de Endocrinologia e Metabologia do Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Brazil.

Address all correspondence to Shehzad Basaria, M.D., 4940 Eastern Avenue, B-Building, Suite 114, Baltimore, MD 21224; E-mail: sbasaria@jhmi.edu

Accepted for publication December 2002.

nation was significant for decreased muscle bulk and power. Pertinent laboratory values are as follows: sodium 149 meq/L, potassium 3.9 meq/L, creatinine 0.9 mg/dL, glucose 92 mg/dL, calcium 7.9 mg/dL, LDH 241 IU/L, uric acid 9.2 mg/dL, hematocrit 33.2%, and WBC 4.1/mm^3. Serum osmolality was 304 mOsm/kg with a concomitant urine osmolality of 67 mOsm/kg and specific gravity of 1.004. A comprehensive endocrine work-up was performed, revealing the following: luteinizing hormone (LH) <0.1 mIU/mL, follicle-stimulating hormone (FSH) = 0.7 mIU/mL, testosterone < 20 ng/dL (normal 400 – 1000), TSH = 1.09 mU/L (0.5 – 4.50), free T4 = 0.6 ng/dL (0.7 – 1.6), prolactin = 18 ng/mL (0 – 20), insulin-like growth factor-1 (IGF-1) ≤ 16 ng/mL (normal 71 – 290), and random cortisol = 5.5 μg/dL. Cosyntropin stimulation test (250 μg of adrenocorticotropin hormone [ACTH] administered intravenously resulted in a serum cortisol level of 10.3 μg/dL (normal 20 μg/dL) at 60 minutes. Urine electrolytes were normal. MRI of the pituitary showed thickening of the pituitary stalk without any other lesions (Figs. 1a and 1b).

Excisional biopsy of the 3.5 cm axillary lymph node was performed. Histopathology was consistent with diffuse, large B-cell lymphoma. The computerized tomography (CT) scan of the chest showed mediastinal and pre-tracheal adenopathy. Abdominal CT scan showed significant celiac adenopathy resulting in compression of the gastric pylorus (explaining patient's post- prandial emesis). Serum angiotensin-converting enzyme (ACE) level (15 IU/L [normal 10 – 34]) and 1.25 vitamin D level (31 pg/mL [normal 15 – 60]) were normal (thus excluding sarcoidosis). Serum and urine protein electrophoresis were normal. It was concluded that the patient's hypophyseal involvement most likely represented metastatic lymphoma. The patient was started on vasopressin analogue (DDAVP) at a dose of 10 μg twice daily intranasally and replacement doses of hydrocortisone (10 mg twice daily), levothyroxine (0.1 mg once daily) and testosterone enanthate (200 mg intramuscularly every two weeks). The patient underwent four cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). After the fourth cycle, his appetite improved significantly, with resolution of his postprandial nausea and vomiting. The patient's polyuria also improved, resulting in a reduction in his DDAVP dose (10 g once daily). A follow-up CT scan showed complete resolution of the mediastinal and abdominal lymphadenopathy. Follow-up MRI of the pituitary gland showed complete resolution of the pituitary stalk thickening (Fig. 2). However, hormonal evaluation of the anterior pituitary showed persistent panhypopituitarism (testosterone < 20 ng/dL, LH = 9.6 mIU/mL, FSH = 3.2 mIU/mL, IGF = 22 ng/mL, cortisol after cosyntropin stimulation test = 16 μg/dL [normal > 20] and TSH = 0.11 μIU/mL). He continued on stable replacement doses of DDAVP, hydrocortisone, levothyroxine and testosterone. Six months later, his disease recurred and the patient failed to respond to additional cycles of chemotherapy. He died 3 months later.

Discussion

In an adult, the diagnosis of pituitary stalk enlargement is entertained when the stalk diameter exceeds 4 mm (1). The differential diagno-

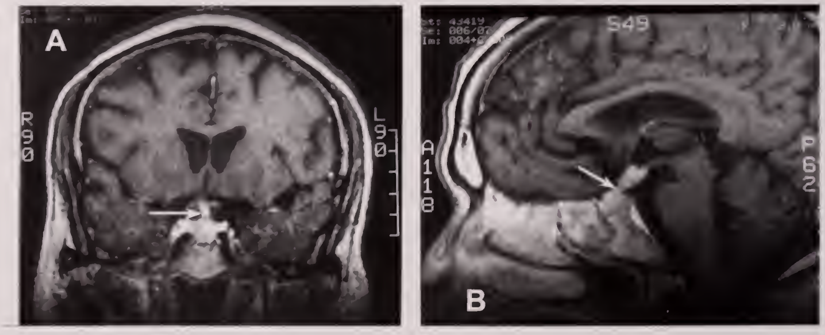

Fig. 1. Coronal (a) and sagittal (b) view of the pituitary stalk (arrows), showing significant enlargement on magnetic resonance imaging.

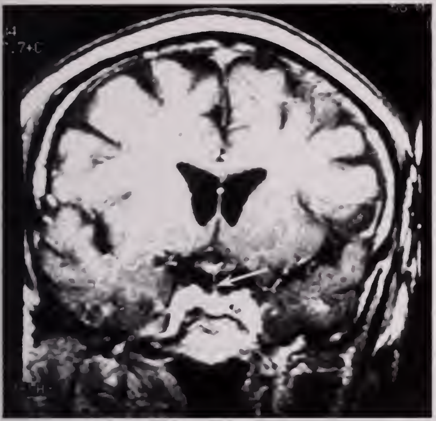

Fig. 2. Coronal view of the infundibulum, which has returned to its normal size (after) after chemotherapy.

sis of pituitary stalk enlargement includes infiltrative diseases like hemochromatosis and sarcoidosis, infectious diseases like tuberculosis and fungal infections, vascular compromise, metastatic solid tumors (including lymphomas) and leukemias (2). According to various reports, pituitary metastases have been reported to occur in 1–27% of patients with cancer (2). Breast cancer in women and lung cancer in men are the most common cancers involving the infundibulum and the posterior pituitary. The presence of DI is an important feature differentiating metastatic lesions from adenomatous lesions of the pituitary gland. Metastatic deposits are lodged more frequently in the neurohypophysis than in the adenohypophysis, due to the nature of the vascular supply of the posterior pituitary. The posterior lobe is supplied by the hypophysial arteries, which are branches of the internal carotid artery. This systemic circulation predisposes the posterior pituitary to become a haven for metastatic deposits compared to the anterior pituitary, which is relatively protected by the sealed circulation of the portal venous system. In patients with lymphoma, DI occurs due to infiltration of the pituitary stalk and/or neurohypophysis. In the majority of these patients, the pituitary function does not recover, despite treatment of the underlying condition. Although our patient did not have any recovery of his anterior pituitary function after chemotherapy, the dose of DDAVP decreased, suggesting an improvement in DI. Diffuse large cell lymphoma of B-cell immunophenotype is known to be the most common lymphoma metastasizing to the pituitary gland and the pituitary stalk. This type of lymphoma is often extremely aggressive and is associated with a high mortality rate. Angiocentric T-cell lymphoma has also been reported to metastasize to the infundibulum (3–5).

References

1. Puig ML, Webb S, Del Pozo C, et al. Endocrine aspects of pituitary stalk enlargement. Clin Endocrinol (Oxf) 1987; 27(1):25–32.
2. Kimmel DW, O'Neill BP. Systemic cancer presenting as diabetes insipidus. Clinical and radiographic features of 11 patients with a review of metastatic-induced diabetes insipidus. Cancer 1983; 52(12):2355–2358.
3. Balmaceda CM, Fetell MR, Selman JE, Seplowitz AJ. Diabetes insipidus as first manifestation of primary central nervous system lymphoma. Neurology 1994; 44(2):358–359.
4. Gottfredsson M, Oury TD, Bernstein C, et al. Lymphoma of the pituitary gland: an unusual presentation of central nervous system lymphoma in AIDS. Am J Med 1996; 101(5):563–564.
5. Ramsahoye BH, Griffiths DF, Whittaker JA. Angiocentric T-cell lymphoma associated with diabetes insipidus. Eur J Haematol 1996; 56(1–2):100–103.

EDITOR'S NOTE

Imaging in Medicine

ADVANCES IN BIOLOGY AND MEDICINE have been nothing short of spectacular. Yet the current frontier depends, in large part, on the labors of earlier pioneers. Which discoveries have been most significant is arguable. Our choices of discoveries would include the following, not necessarily in temporal sequence: The experiments and observations by Harvey on the circulation; Jenner's use of cowpox to vaccinate against smallpox; the development of the microscope by Leeuwenhoek; the innumerable observations on bacterial diseases and rabies by Pasteur; Semmelweiss' insight into the cause of puerperal sepsis; Fick's physiologic principle that bears his name; Virchow's organization of the systematic study of pathology; Mendel's insight in genetics; Koch's discovery of *Mycobacterium tuberculosis*; and the accomplishments of many others such as Welch, Libman, Landsteiner, Starling, Otto Frank, Ehrlich, Einthoven, the Curies, Roentgen, Osler, Richard Lewissohn, Schick, Rabi, Banting and Best, Homer Smith, Pauling, Hodgkin and Huxley, Watson and Crick, Fleming, Florey, Salk, Sabin, Berson and Yalow, Sutherland, Gilbert and Goldstein, and Furchgott.

We have not included the more recent advances, since readers can pick and choose their own from a list of names of Nobel laureates and of recipients of other major awards, and the recent biomedical literature. We apologize if we have omitted names that any reader considers more significant. Our purpose in reprinting the following articles, however, is to highlight the contributions of individuals whose names and work have been forgotten, denied, or lost. This is not to say that this work and observations are comparable to that of Pasteur, Watson and Crick, and Berson and Yalow. But there is no doubt in our minds that this work can be considered the first to demonstrate the clinical importance of imaging techniques which now detail the anatomy and quantify the function of organs, tissues, and cells, not previously appreciated, even at surgery or autopsy.

Dr. Moses Swick is the author of the landmark article which is being republished in this issue of *The Journal*. The original report appeared in 1929 in German.

Dr. Swick describes his search for and successful use of an iodine-containing contrast compound which made possible the relatively noninvasive simultaneous delineation of the renal anatomy and the evaluation of renal function. This was no small feat. This test was known originally as the intravenous pyelogram, and by some as the "Swick" test. Crude as the test was, it represented a major advance in the diagnosis of kidney disease. Additional illustrations of some of the original roentgenograms are shown in the republished article by Jaches which follows. While the test has been supplanted, it nonetheless ushered in the era of functional imaging. Since Dr. Swick's remarkable discovery, a safer, non-ionic, intravenous, iodinated contrast material has been developed and is now almost universally utilized. Intravenous contrast applications have dramatically expanded since the introduction of angiography and computed tomography. Today, utilizing multidetector CT technology, contrast enhanced lesions as small as several millimeters can be easily detected and biopsied percutaneously. Noninvasive coronary artery and vascular imaging is becoming a reality that Dr. Swick could only have imagined.

Dr. Swick graduated from the Columbia University College of Physicians and Surgeons and was a house officer at The Mount Sinai Hospital. Upon completion of his house staff training he accepted a Libman Fellowship offered by the Hospital to study abroad. In those days, The Mount Sinai Hospital offered this fellowship, and many others, to support the growth, development, and expertise of promising young clinicians. This program of privately supported fellowships long antedated the national effort to promote the training of clinical investigators and practitioners. It is testimony to the commitment of the institution and its leaders to professional education and, thereby, to the high quality of patient care at this hospital and elsewhere, wherever the recipients were destined to be appointed.

Sherman Kupfer, M.D.
Zvi Lefkovitz, M.D.
The Mount Sinai Journal of Medicine

Reprinted from The Journal of the American Medical Association
Nov. 8, 1930, Vol. 95, pp. 1403–1409

Intravenous Urography by Means of the Sodium Salt of 5-Iodo-2-Pyridon-N-Acetic Acid*

Moses Swick, M.D.
New York

In 1923 Rowntree and his co-workers (1) of the Mayo Clinic were the first to attempt to visualize the urinary tract by means of the intravenous injection of a 10 per cent solution of sodium iodide and also by the oral administration of that salt. The urinary bladder, and in some cases the pelvis and ureter, could be visualized.

The following year Rosenstein and von Lichtenberg (2) reported at the urologic congress in Berlin their results, repeating the work of Rowntree and his co-workers with sodium iodide but in conjunction with perirenal pneumoradiography.

In the same year Volkmann (3) reported his observations with the use of different halogen compounds; he found the intravenous injection of a 10 per cent solution of sodium iodide to be best.

In 1927 Lenarduzzi and Pecco (4) tying off the ureter and injecting sodium iodide intravenously in animals, obtained positive roentgenograms of the kidney, pelvis and ureter.

Hryntschak (5) at the urologic congress in Berlin in 1928 and in a publication in 1929 (6) reported his results with the use of a large series of bromine and iodine compounds, aromatic in nature, carrying out about 200 animal experiments. Neither the names nor the chemical formulas of the substances used by him are stated. In his publication the only detail of the chemical composition of three of them applied and numbered 13, 27 and 48 is that the first two were iodine and the last a bromine compound. In some of his experiments he simultaneously used an adjuvant, such as caffeine, urea, pituitary extract and atropine, to influence excretion and the dynamics of the pelvis and ureter. He obtained some positive results in animals and in a female patient. In his conclusions he stated that although, two and a half years ago, he had been able to obtain useful intravenous pyelograms in a few cases, the method had by no means met the conditions set forth by him. He, however, expressed the hope of accomplishing his alms by continued investigations.

Ziegler and Köhler (7) reported at the urologic congress in Munich in 1929 and in a publication in 1930 (8) their results with the oral administration of 10 Gm. of sodium iodide and 10 Gm. of urea in milk in conjunction with pressure applied over the sacro-iliac articulation through the abdominal wall by means of a special apparatus.

All investigators who utilized the halogen compounds found that they could not be given in sufficiently large quantities to be of practical value in visualizing the urinary tract, though under favorable conditions in occasional cases, the kidney, pelvis, calices and ureters could be made out.

Roseno (9) was the first to achieve practical results by means of the intravenous use of a

---

*Read before the Section on Urology at the Eighty-First Annual Session of the American Medical Association, Detroit, June 27, 1930. The original article did not contain all figures, owing to a lack of space. This republication contains all figures, as depicted in the author's reprints.

This work was carried out with the aid of a grant from the Emanuel Libman Fellowship Fund. It was initiated at the Staedtisches Krankenhaus, Altona, Germany (Prof. Dr. Leopold Lichtwitz, director), continued in the urologic service of the St. Hedwig Krankenhaus, Berlin (Prof. Dr. Alexander von Lichtenberg, director), and has since been pursued in the urologic service of Dr. Beer, the radiologic department of Dr. Jaches, and the Chemical Laboratories of The Mount Sinai Hospital, New York.

Reprinted from *JAMA* 1930; 95:1403–1409, copyright 1930, with permission from the American Medical Association.

combination of sodium iodide and urea, called "Pyelognost" [NaI, $CO(NH_2)_2$]. According to some reports it is stated that the substance employed by him is at times associated with reactions. The visualization of the urinary tract, however, is satisfactorily accomplished. Roseno also stressed the functional aspects of the problem. He gave an account of his investigations at the urologic congress in 1928. In 1929 he made a further presentation of his work before the urologic congress in Munich and published an extensive report of the method and the results. In the course of a discussion at the time of the first presentation, von Lichtenberg (10) expressed himself pessimistically concerning the possibility of intravenous urography.

This work (11) was begun with N-methyl-5-iodo-2-pyridon, synthesized by Professors Binz and Räth.

Formula 1

At the wish of Professor Binz, the efficacy of this substance in the therapeusis of streptococcus was under investigation in the clinic of Professor Lichtwitz in Altona, Germany. The study of its excretion through the kidney and into the bile and its iodine content (54 per cent) led to the thought that the substance might be applicable for roentgenologic purposes. Experiments on rabbits demonstrated the fact that the kidney parenchyma and urinary bladder could be visualized after the intravenous injection of the drug; the pelvis and the ureter, on the other and, were poorly seen. Ligation of the latter, however, did bring the upper tract well into view. The gallbladder was not visualized. Simultaneous studies of its excretion, limited to determinations of the iodine component, revealed about 75 to 80 per cent of the injected iodine in the urine in from twelve to sixteen hours.

Concerning the toxicity and tolerance, I found that 0.2 Gm. per kilogram of body weight could be administered intravenously to the rabbit without any demonstrable ill effects; 0.33 Gm. per kilogram, however, produced transient generalized disturbances. On the basis of these observations, one could theoretically give to a 60 kilogram individual 18 Gm. of the substance as a maximal dose. Because of marked individual differences in man, the quantity administered was far below the calculated one. The adult received 6 Gm. of substance. Headache, nausea, vomiting, generalized discomfort, and in two cases transient diplopia were disturbing factors. The oral and rectal administration of this drug also yielded similar roentgenologic results and toxic manifestations. In all cases the urinary bladder was seen. The kidney parenchyma itself appeared to stand out more in relief. In man, the upper urinary tract was outlined only after producing a temporary artificial obstruction in the ureter by means of a bougie at the time of maximal excretion. The attained results, though not sufficiently good for practical purposes, were encouraging and pointed to the possibilities of further development.

The experience with this substance brought out the need for a modification, possessing better tolerance and greater solubility, so that a larger dose could be administered. In this way, a higher concentration of the excreted iodine component could be hoped for. The observation of double vision and the possibility that the methyl radical might be responsible were noted. At a conference between Professor Binz and his associates, Professor Lichtwitz and me, these results and observations were presented. Professor Binz, who followed these investigations with great interest, said that he felt that these needs could be fulfilled. He supplied us with several compounds which he states belonged to the selectan group, synthesized by him and Professor Räth at an earlier date, and which now were prepared in larger amounts for our purpose and studied with the aid of Dr. Hillgruber (12). One of them, insoluble in water, was soluble in very strong alkali. It could not be given intravenously and was therefore administered by mouth to a dog and in gelatinum duratum capsules to a male patient at Professor Lichtwitz's clinic with negative results. Professor Binz had furnished me with this drug one week before the conference mentioned.

Thereafter I continued the work in the urologic service of Professor von Lichtenberg in Berlin. To eight patients, 7.5 Gm. of the original substance, N-methyl-5-iodo-2-pyridon, were given by mouth with the already described reactions. The outline of the bladder was seen. Only in one case, that of a stone obstruction of the ureter about one inch below the ureteropelvic junction, was a useful roentgenogram of the pelvis and ureter above the stone obtained. The insoluble compound used at Professor Lichtwitz's clinic was now tried again at Professor von Lichtenberg's division with the same negative results. Another compound of this group, having a higher iodine content and a sodium acetate radical substituted for the methyl, was then tried. Though more soluble than the previous one, it was still unsuitable for intravenous application. The oral administra-

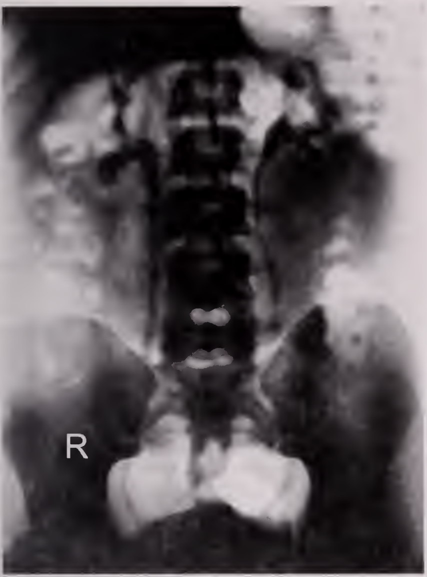

Fig. 1. Right-sided bifid pelvis in a man, aged 20; 40 Gm. of substance.

tion was likewise inadequate because of the poor absorption by the gastrointestinal tract. When a preparation having a lower iodine content and the sodium acetate group substituted for the methyl was furnished by Professor Binz, the clinically applicable and successful substance, 5-iodo-2-pyridon-N-acetate of sodium, was finally obtained. This compound differs from the original only in the substitution of sodium acetate in place of the methyl group. It was fortunate that this preparation, introduced abroad as "Uroselectan," proved to be free from all accompanying reactions, to have quite an extraordinary affinity for the kidney, and to be very soluble in water. These needs were therefore completely fulfilled and satisfactory roentgenograms could now be obtained, as reported by me at the urologic congress in Munich in 1929 (11). Professor von Lichtenberg, who took up the subject directly after me, stated that he considered that which had been communicated a significant advance (13). Some weeks later, my paper was published in the *Klinische Wochenschrift* and was followed by another contributed by Professor von Lichtenberg and me (14).

The 5-iodo-2-pyridon-N-acetate of sodium (42.2 per cent iodine) is nontoxic, very soluble in water and neutral in its reaction.

Formula 2

The iodine in the molecule exists in a stable organically bound state. Neither in the injected solution nor in its excreted form is iodine present in ionized state. These facts, despite the relatively large quantity of iodine in the amount of this substance that can be administered with impunity, would seem to explain, at least empirically, why iodism has never been observed. The tolerance for this compound is exceedingly great. A rabbit would receive 3 Gm. per kilogram of body weight without any harm. With the latter dose as a basis of calculation, it follows that 180 Gm. of the substance, or, in terms of iodine, 75.6 Gm., can be theoretically administered to a 60 kilogram person. The substance is excreted as such through the urinary tract, being recovered from the urine as the light yellow, insoluble acid on the addition of a dilute mineral acid. Because of the relative simplicity and accuracy and because I found it to be of assistance in the evaluation of the roentgenologic results, it has been considered feasible to apply a quantitative determination of this insoluble, precipitated acid-form as a basis for a test of renal function.

The recovery and identification of the excreted substance have been established in the following manner:

The addition of a dilute mineral acid — HCl or H_2SO_4 — to urine containing the excreted soluble salt of the 5-iodo-2-pyridon-N-acetic acid results in the precipitation of the insoluble acid form. The precipitating agent should be added gradually until no more precipitation occurs. After one hour's settling the insoluble acid is filtered by means of suction on a Buchner funnel and is washed free from the precipitating agent with distilled water, as determined by the silver nitrate test for hydrochloric acid or the barium chloride test for sulphuric acid. The residue is dried to a constant weight at 80°C. For identification, a variety of samples of the urinary precipitate were analyzed for their iodine and nitrogen content; their acid equivalents and melting points were also determined. These were simultaneously controlled by comparison with similar determinations on substance precipitated from clean manufacturer's samples of the sodium salt. The results obtained are presented in Table 1.

Another series of melting point determinations (uncorrected) on twenty-four individual

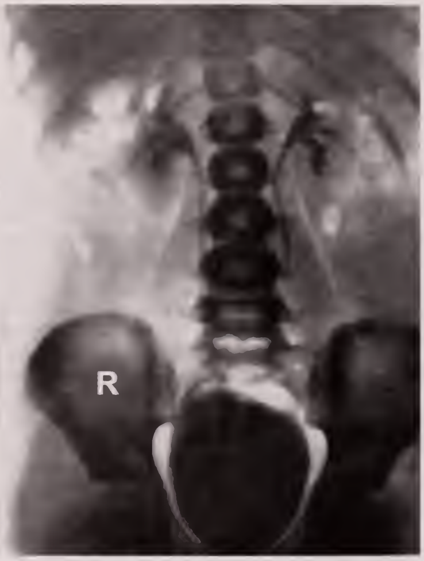

Fig. 2. Intravenous urogram to exclude right urinary calculus, in a girl, aged 8 years. Slight dilatation of right kidney pelvis and blunting of calices (pyelitis). 25 Gm. of substance.

urinary precipitates yielded the following results: four times 236°C, five times 237°, four times 238°, four times 239°, four times 240°, two times 241°, one time 242°C. The control of precipitates from two manufacturers' samples simultaneously determined were 239° and 240°C. (The acid melts with decomposition. The determinations represent melting points of samples of different urines and colors, varying from light yellow to brown, made with the same rate of heating.)

The brown color of the precipitate, recovered from some of the urines, is believed to be due to the admixture of urinary pigment; this is demonstrated as follows:

1. If animal charcoal is added to boiling water containing the brown colored acid-form in solution, the recrystallized substance no longer is brown; it now is light yellow, resembling pure precipitate.

2. Conversely, when a manufacturer's sample of the solution of a sodium salt is added to normal urine and then the acid-form precipitated from it (a procedure analogous to that of the recovery of the substance from the urine), the precipitate obtained is then brown. The same pure solution, however, with the addition of acid alone, yields a light yellow precipitate.

3. Qualitative analysis of the precipitate, following the scheme for the examination of urinary calculi, is negative for nonpigmentary urinary constituents.

The next consideration is whether the precipitation is quantitative. To determine this, two-hour urine specimens of patients injected with a known amount of the sodium salt were collected. On each specimen two simultaneous determinations were made, one for its iodine content by a sodium carbonate and sodium nitrate fusion method; the other by precipitating the acid and determining its constant weight. Since the acid by molecular weight contains 45.5 per cent of iodine, the quantity of iodine found by multiplying the weight of the precipitated acid by 45.5 should correspond to that of the total iodine de-

TABLE 1

Analysis of Urine Containing Excreted Soluble Salt of 5-Iodo-2-Pyridon-N-Acetic Acid

		Nitrogen Determination Micro Dumas Method	Iodine Determination Na_2CO_3 + $NaNO_3$ Fusion Method	Iodine Determination Carius Method	Acid Equivalent	Melting Point Uncorrected
Sample	Color					
Manufacturer sample	Light yellow white	4.99%	46.77%	46.37%	277	235
Urine sample 1	Light yellow	5.23%	46.23%	46.4%	280	234 white
Urine sample 2	Slightly brown	5.04%	46.31%	47.98%	Not done	Not done
Urine sample 3	Brown	5.29%	46.65%	50.1%	279.5	235

Note: The determinations in columns 4, 5 and 6 represent averages. Theoretical iodine content, 45.5%; theoretical nitrogen content, 5.02%; theoretical acid equivalent, 279.

termined directly from the urine. Tables 2 and 3 illustrate the results obtained.

Comparing columns five and six, that is, the calculated iodine values with the independent iodine determinations, one observes a constant, close agreement. The reason for the relatively small differences between the calculated (the lower values in column 5) and the quantitatively determined iodine (column 6) can be explained by the presence of the precipitated acid-form in the filtrate as a result of its slight solubility. It has been found that the iodine content of the filtrate plus the calculated iodine compare very favorably with that of the quantitatively determined iodine. There were isolated cases in which there were discrepancies, believed, however, to be due to an error in the technic of iodine determination. This phase is being investigated further.

Finally, in order to establish the percentage excretion of the iodine and of the precipitated acid, it is necessary to determine the actual amount of injected salt in terms of the iodine component, and also in terms of the precipitated acid. It is obvious that, in the preparation of the solution, losses will occur. The following are the factors and sources of error which should be considered:

1. Apothecary scale used — about 2 per cent.
2. Loss due to the moisture content of the salt — about 3 per cent.
3. Loss through double filtration of the solution — about 3 per cent.
4. An indeterminate loss due to the impossibility of a quantitative transfer of the 40 per cent solution from the glassware used in its preparation.

TABLE 2

*Quantitative Determination of Urine Specimen**

Urine Specimen	Volume Cc.	Specific Gravity	Weight of Precipitated Substance Gm.	Iodine Calculated from Substance Gm.	Iodine Determination of Urine Gm.
2 hours	850	1.014	19.79	0.004	9.6295
2 hours	200	1.034	9.395	4.275	4.76
2 hours	120	1.032	4.604	2.095	2.4578
2 hours	91	1.024	1.792	0.8154	1.0396
2 hours	93	1.014	No precipitate		
2 hours	150	1.008	No precipitate		
Total grams			35.581		17.889
Percentage of substance excretion					91.23
Percentage of iodine excretion					95

*A woman, 25, with good renal function; 50 Gm. of Substance injected.

TABLE 3

Quantitative Analysis of Urine Specimen in a Case Presenting Poor Function.

Urine Specimen	Volume Cc.	Specific Gravity	Weight of Precipitated Substance Gm.	Iodine Calculated from Substance Gm.	Iodine Determination of Urine Gm.
2 hours	335	1.019	6.70	3.05	3.12
2 hours	260	1.022	6.10	2.78	2.84
2 hours	145	1.025	3.86	1.76	1.82
2 hours	100	1. 025	3.56	1.62	1.79
2 hours	138	1.022	2.71	1. 23	1.26
Total grams			22.93		10.83
Percentage of substance excretion					53
Percentage of iodine excretion					52

A woman, aged 42; 55.5 Gm. of Substance injected.

5. The difference in molecular weight of the sodium salt (301) and the precipitated acid (279), 7 per cent.
6. Loss due to the solubility of the precipitated acid, a fraction of 1 per cent.

Thus, to establish the extent of inaccuracy in the quantity of iodine actually administered as against its theoretical content, a solution as for injection was prepared. Its actual iodine content, determined chemically, was found to be on the average 89 per cent of the theoretical. This figure can be designated as "the iodine factor."

The method for establishing the "precipitated acid factor" was similar to the foregoing except that the prepared solution was then distributed among normal urines so that each two-hour specimen resembled approximately in its volume and substance content those excreted by patients injected with different amounts of the solution of the sodium salt. (In carrying out the renal function test by means of the quantitative estimation of the excreted substance, five or six two-hour urine specimens are collected.) Table 4 demonstrates the average established factor; namely, from 77 to 78 per cent.

In other words, to establish the basic acid value, 22 per cent is to be deducted from the theoretically administered weight of sodium salt when calculating the percentage of excretion in terms of acid substance. Similarly, 11 per cent is to be deducted from the theoretical iodine content of the injected sodium salt in order to estimate the percentage excretion in terms of the iodine component.

These aspects being clarified, it now becomes evident that quantitative determinations of the excreted substance in terms of the precipitated acid can form the basis of a test for renal function. (The quantitative estimation of the precipitated acid has been chosen in preference to that of the iodine because of its relative simplicity and reliability.) Normally about 85 to 95 per cent of the substance can be recovered from the urine within from eight to twelve hours after the injection. In two cases 98 per cent was recovered. From that period on, under normal conditions, as a result of the solubility of the precipitate, which during this stage occurs in such small amounts, its presence can be detected only by an iodine determination method. It is thus found that the excretion of very small amounts of the substance goes on from three to

TABLE 4

Corrected Acid Substance: Factor for Calculating Percentage of Excretion

Druggist Scale	Chemical Scale	Per Cent of Loss
1. 40 Gm. of substance	39.523 Gm.	–1.19%
2. Drying	38.2 Gm.	–3.35%
3. Solution of 100 cc. filtration (Loss on filter paper = 1.125 Gm.)		–2.95%
4. Aliquot for iodine determination, 4 cc. of total 96 cc.		
5. Distribution on basis of average urinary output by volume and by weight		

Specimen	Volume Cc.	Containing Approximately	Gm. Precipitated Acid Recovered
A. 2 hrs.	550	1/2 solution precipitated and filtered	16.96
B. 2 hrs.	175	1/4 solution precipitated and filtered	8.19
C. 2 hrs.	150	1/10 solution precipitated and filtered	3.515
D. 2 hrs.	90	1/20 solution precipitated and filtered	1.555
			29.850
Aliquot 4 cc.			1.24
			31.090
Acid substance factor (apothecary scale).			$\frac{31.09}{40.0} = 77.7\%$
Acid substance factor (chemical scale).			$\frac{31.09}{39.525} = 78.66$

This factor is variable within narrow limits depending on points enumerated ten and perhaps more days after the injection. For example:

First twenty-four hours, 850 cc., 0.3195 Gm. of iodine.
Second twenty-four hours, 1,200 cc., 0.0218 Gm. of iodine.
Third twenty-four hours, 1,400 cc., 0.0036 Gm. of iodine.
Fourth twenty-four hours, 1,400 cc., none.

From the results already obtained, it is seen that the normally functioning kidney possesses the ability to excrete this substance in a relatively large quantity within a given short period. This may be characterized as the thrust excretion ability of the normally functioning kidney," present during the first two hours. To illustrate, from about 45 to 65 per cent of the total precipitable acid is recovered during the first two hours, about 20 to 33 per cent during the next two, and the remainder during the subsequent hours. Figure 3 illustrates the curves of excretion in a normally functioning and in a poorly functioning kidney.

Aside from the dose administered and the extrarenal factors influencing renal secretion, the thrust excretion ability of the normally functioning kidney plays a vital role in determining good roentgenologic visualization. During the later periods, in spite of the fact that the substance is still being excreted, poor or no visualization is obtained. Good visualization is dependent on a definite concentration of the shadow-producing element determined by the factors enumerated. When the additional mechanism of obstruction is present, visualization may be had although the normal height of excretion is absent, provided excretion takes place. On the other hand, under the same circumstances but with normal excretion, intensification of the shadow results. Thus, in a general way, it may be said that visualization, poor visualization, or no visualization is dependent on the functional activity of the kidney, in other words, its concentrating ability, as well as on extrarenal factors.

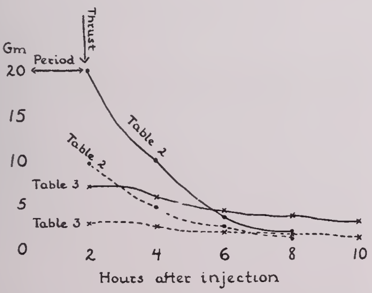

Fig. 3. Excretion of normal and of abnormal kidneys, 50 Gm. dose, tables 2 and 3: solid line, weight of precipitable acid excreted, in grams; broken line, weight of iodine excreted.

However, of the 122 cases studied at The Mount Sinai Hospital, one unexplainable exception has been noted. A woman, aged 54, with pain in the back and left kidney region, had an intravenous urogram done, June 2, 1930. Visualization was absent on the right side in all plates. The left urinary tract appeared normal. A large shadow of what looked like kidney was seen in the right upper quadrant. A faint curvilinear shadow in the bony pelvis on the right side was also observed (ureter?). June 4, cystoscopy and a right retrograde pyelogram revealed normal indigo carmine from both sides as well as the presence of a right sacral kidney. In order to gain an insight into this discrepancy, another intravenous urogram was repeated about two and one-half weeks later. The right kidney pelvis again was not visualized though the ureter could be definitely seen. This example serves to illustrate the need for caution in passing final judgment with absolute certainty on the functional state of the kidney by this method alone.

Moreover, it is also important to bear in mind that the functional activity of the kidney may be temporarily or permanently inhibited, and that the mere nonvisualization at a given examination does not necessarily signify permanent renal damage. The following case is illustrative:

Cystoscopic examination of a man, aged 41, was done, and a left retrograde pyelogram was made. At that examination normal indigo carmine excretion from both ureters was observed. The left pyelogram was normal. Following this examination, hematuria and marked pain in the left loin set in and persisted for about one week. When both symptoms had subsided, intravenous urography was done. Absent visualization of the pelvis and ureter with good kidney outline on the left side and a double pelvis and forked ureter on the right were noted. However, another intravenous urographic examination, about three months later, revealed a normally functioning and appearing left urinary tract in addition to the previous observations on the right; in other words, a case of temporary functional inhibition following retrograde pyelography.

Therefore, to evaluate intravenous urography and to interpret correctly the results ob-

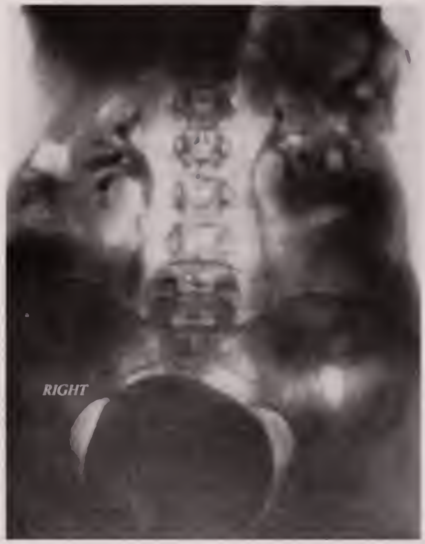

Fig. 4. Intravenous urogram to exclude a right renal neoplasm in a woman, aged 48. Demonstrates ptosed kidney, ureteral kink with dilatation. 50 Gm. of Substance.

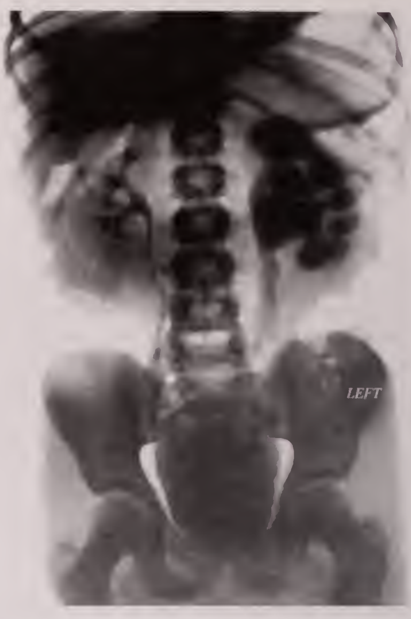

Fig. 5. Marked dilatation of ureter, kidney pelvis and calices in a boy, aged 10 years. 25 Gm. of substance. (Case of Drs. Leopold and Stewart of the Lenox Hill Hospital, New York.)

tained from it, it is of paramount importance to consider this method as an excretory one and to bear constantly in mind the processes occurring in the renal and extrarenal systems.

As an adjuvant in assisting one to interpret and to evaluate the radiologic results, it is felt that simultaneous determinations of the substance recovered in the urine as described are sometimes helpful. It is not assumed that this test is superior to other tests of renal function; but, in view of its relative simplicity and the fact that it forms part of the intravenous examination, its use is advocated solely as a confirmatory aid in the interpretation of the intravenous urogram.

The blood urea, phenolsulphonphthalein, the indigo carmine, and the dilution and concentration tests are of great assistance in establishing the contraindication to the application of this method in a given case of bilateral advanced kidney disease. Where the blood urea is high and the concentrating power of the kidney poor, the method yields few anatomic data and becomes not only superfluous but perhaps attended by danger. For information of renal function under such circumstances, more simple and less expensive means, such as the blood urea and phenolsulphonphthalein determinations, serve the purpose.

In addition to anatomic data derived by this physiologic procedure, another vitally important phase of the urinary tract that can be studied without the introduction of instruments is the functional dynamic activity of the pelvis, ureter and bladder.

Method of Administration

For an adult, the usual dose, 40 Gm. of substance, is added in small quantities to doubly distilled water, which has been previously warmed to a moderate degree so that the resultant volume is about 100 cc. Stirring aids the process of dissolving. The solution is filtered twice through ordinary filter paper into a 250 cc. clean Erlenmeyer flask, which is preferably stoppered with fresh wax paper. It is then sterilized in a water bath for half an hour or autoclaved at 15 pounds pressure for twenty-five minutes. The syringe method, in preference to that of the gravity, is chosen, in the feeling that it is more apt to avoid the possibility of a foreign

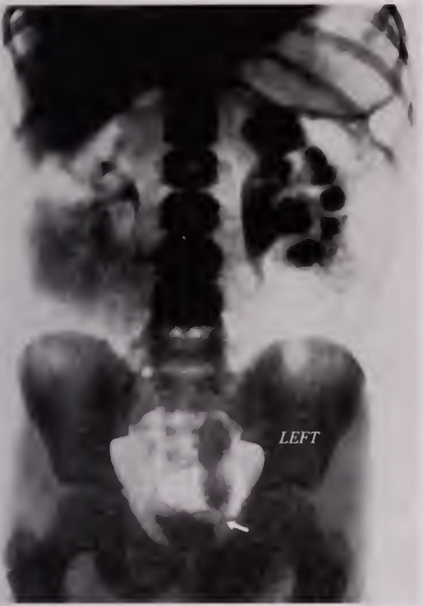

Fig. 6. Same patient as in figure 5, with bladder partially empty, now demonstrating stricture (congenital) ureterovesical junction with marked dilatation of lower part of ureter, which was hidden on previous film by distended bladder. (Case of Drs. Leopold and Stewart of the Lenox Hill Hospital, New York.)

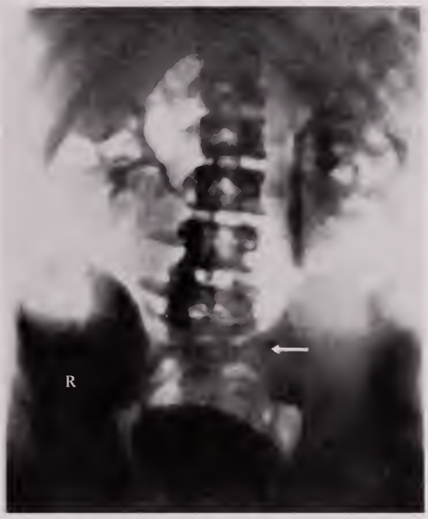

Fig. 7. Impassable stone obstruction, lower third of the left ureter, in a boy, aged 19. Intravenous urogram — good function — showing dilated ureter, pelvis and calices above stone. Right side normal. 50 Gm. of substance. Arrow points to stone.

body reaction. A sufficient number of record syringes plus injection needles is sterilized in distilled water. The injection is done in two or three stages at intervals of from three to five minutes. The first roentgenogram is usually taken about fifteen or twenty minutes after the last injection. The subsequent three plates are made about twenty-five minutes apart. When functional disturbances are present, it is advisable to have additional later plates, at approximately one to three hour intervals, taken to determine definitely the absence of visualization, or the presence of late visualization. Particularly in those cases in which there is the added factor of obstruction — ureteral stone, prostatic enlargement, or ureteral strictures — there may be a late, but good or poor type of visualization. Experience alone will guide one in the interpretation of the plates, as well as the number of plates that may be necessary.

An added factor of great importance which has improved the results as far as density, clarity and consistency of shadow are concerned has been the application of a moderate degree of compression by means of an air-inflated rubber balloon (basket ball bladder), maintained over the urinary bladder region for from five to ten minutes prior to and during the taking of each roentgenogram. It is also advisable to take one or two plates without compression several minutes after any of the preceding ones and to have the patient empty his bladder after the second or third plate.

From studies controlled on the same patient with different doses several days apart, the impression gathered is that the administration of a 50 to 60 Gm. dose of substance in 40 per cent concentration, given in divided portions at about a ten-minute interval, yields denser and clearer roentgenograms. However, in view of the fact that this increased dosage means additional expense and that with a 40 Gm. dose sufficiently good practical results are usually obtained, particularly with compression, this change is at present advocated with some reserve. A 20 Gm. dose in adults has also given positive results.

The doses (40 per cent concentration) for children are as follows: 13 years of age, from 25 to 30 Gm.; 9 years and up, 25 Gm.; 6 years and up, 20 Gm.; 4 years and up, 16 Gm.; 2 years, 14 Gm.; 6 months, from 10 to 12 Gm.

Reactions

During the injection the patients experience transient thirst and generalized warmth, particularly involving the face and bladder regions. Nausea and vomiting of transient duration have occurred twice. Occasionally there is pain up the arm of injection, which, however, disappears shortly afterward. Paravenous infiltration produces pain but no necrosis. Thrombosis at the site of the injection has not been observed. The urine does not reveal any evidence of renal damage by the substance.

Application

The field of application of intravenous urography is evident whenever cystoscopy, ureteral catheterization or retrograde pyelography is dangerous or impossible for infectious or mechanical reasons, and whenever these procedures in general are indicated. The method, aside from offering a bilateral urogram, is also helpful in the presence of hematuria, in cases of implanted ureters, in children, and in individuals in whom instrumentation is taxing and harmful.

Contraindications

Patients with uremia or latent uremia, as determined by the usual clinical methods, do not lend themselves to the application of this method. It is therefore wise to precede the examination by a determination of the blood urea. Experience with hyperthyroid patients is still wanting. The drug in cases of pulmonary tuberculosis does not seem to have any deleterious effect.

For pyeloscopic purposes this method will be feasible only when the density of the excreted substance is sufficiently great. When the function is poor, pyeloscopic results will be correspondingly deficient.

In my original paper published in the *Klinische Wochenschrift* in November, 1929, I (11) stated that the iodine component could not be demonstrated in the circulating blood. In the report by Heckenbach (15) from von Lichtenberg's clinic, Tourné and Damm have shown this to be incorrect. Studies which I was making at the time confirmed their observations. I could detect its presence in the blood as late as ten hours after a 50 Gm. dose. The stools and sputum of the patients injected show the presence of the iodine component in relatively small amounts. In the stool this element could be detected in a bowel movement as late as three to four days. It is also

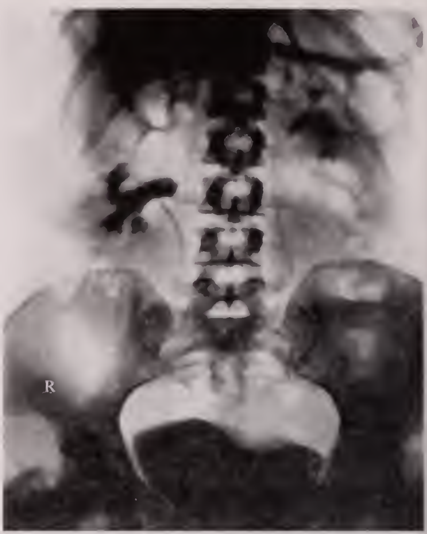

Fig. 8. Ptosis of right kidney, dilatation of pelvis and twist of ureter behind pelvis, in a woman, aged 28. 50 Gm. of substance.

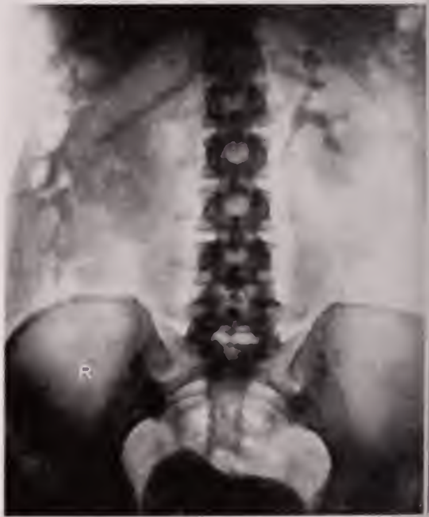

Fig. 9. Intravenous urogram of a woman, aged 45, showing nonfunctioning sacculated right kidney, proved at operation to be a tuberculous pyonephrosis. Retrograde pyelogram impossible. Ureter could not be entered. Left side normal 40 Gm. of substance.

of interest to note that the skin of rabbits injected intravenously with a solution of the substance contained the iodine component.

In closing, I wish to express my deep sense of obligation to Dr. Emanuel Libman and to the directors of the Emanuel Libman Fellowship Fund with whose aid this work was made possible. I am extremely grateful to Professor Binz for his untiring help and cooperation. I am deeply indebted to Professor Lichtwitz for the invaluable aid and facilities which he placed at my disposal. I thank Professor von Lichtenberg for the opportunity and facilities, and also Dr. Rave, the roentgenologist of the St. Hedwig Krankenhaus in Berlin, for his aid. I am also thankful to Drs. Beer, Jaches, Gross and Sobotka, in whose departments at Mount Sinai Hospital this work was further developed, and to the Schering-Kahlbaum Corporation of Berlin, Germany, for its aid and supply of material. I am appreciative of the courtesies extended me by Drs. Bumpus and Alcock, and the members of the Section on Urology of the American Medical Association.

Dr. Moses Swick

1 East One Hundredth Street.

References

1. Osborne ED, Sutherland CG, Scholl AJ Jr., Rowntree LG. Roentgenography of urinary tract during excretion of sodium iodide. JAMA 1923; 80:368–373.
2. Rosenstein P, von Lichtenberg A. In discussion, Verhandl d deutsch Gesellsch f Urol 1924; 6:320–321.
3. Volkmann J. Zur roentgenographischen Darstellung der Harnwege durch intravenöse Verabreichung schattengebender Mittel Deutsche med Wchnschr 1924; 50:1413–1414.
4. Lenarduzzi G, Pecco R. Inienzioni endovenose di ioduro di sodio. Arch ital di radiol 1927; 3:1055–1060.
5. Hryntschak T. In discussion of Roseno's presentation. Zur roentgenographischen Nierendarstellung und Pyelographie auf intravenösem Wege. Verhandl d deutsch Gesellsch f Urol 1928; 8:434.
6. Hryntschak T. Studien zur roentgenologischen Darstellung von Nierenparenchym und Nierenbecken auf intravenösem Wege. Ztschr f Urol 1929; 23:893–904.
7. Ziegler J, Köhler H. Über perorale Pyelographie. Verhandl d deutsch Gesellsch f Urol 1929; 9: 344–345.
8. Ziegler J, Köhler H. Perorale Pyelographie. Med Klin 1930; 26:10–11.
9. Roseno A. Studien zur intravenösem Pyelographie. Verhandl d deutsch Gesellsch f Urol. VIII Kongress, Berlin. 1928; 8:431–433; Intravenöse Pyelographie. Verhandl d deutsch Gesellsch f Chir. LIII Kongress, Berlin. 1929; 53:64–66; Die intravenöse Pyelographie. Verbandl d deutsch Roentgenges. XX Kongress. 1929; 20:73–75; Roseno A, Jepkens H. Die intravenöse Pyelograpbie. Fortschr a d Geb d Roentgenstrahlen 1929; 39:859–863. Roseno A. Die intravenöse Pyelographie. Klin Wchnschr 1929(June); 8:1165–1170. 1929(Aug); 8:1623. Die intravenöse Pyelographie. Verhandl d deutsch Gesellsch f Urol. IX Kongress, Munich. 1929; 9:337–343.
10. Von Lichtenberg A. In discussion of Roseno's presentation. Verhandl d deutsch Gesellsch f Urol 1928; 8:435. VIII Kongress, Berlin.
11. Swick M. Darstellung der Niere und Harnwege im Roentgenbild durch intravenöse Einbringung eines neuen Kontraststoffes des Uroselectans. Verhandl d deutsch Gesellsch f Urol. IX Kongress, Munich. 1929; 9:328–331; Klin Wchnschr 1929(Nov); 8:2087–2089.
12. Medizinische Mitteilungen. Schering-Kahlbaum. February, 1930.
13. Von Lichtenberg A. Klinische Prüfung des Uroselectans. Verhandl d deutsch Gesellsch f Urol. IX Kongress, Munich. 1929; 9:332–336.
14. Von Lichtenberg A, Swick M. Klinische Prüfung des Uroselectans. Klin Wchnschr 1929(Nov); 8:2089–2091.
15. Heckenbach W. Funktionsuntersuchungen bei der Ausscheidung des Uroselectans. Klin Wchnschr 1930(April); 9:684–689.

Reprinted from The Journal of the American Medical Association
Nov. 8, 1930, Vol. 95, pp. 1409–1412

Intravenous Urography (Swick Method)*

LEOPOLD JACHES, M.D.

THE HISTORY OF THE DEVELOPMENT of this method and the chemical and pharmacologic properties of the substance employed are dealt with in greater detail in the paper by Dr. Swick presented before the Section of Urology.

Swick states that the present substance, prepared by Professors Binz and Räth, is nontoxic, very soluble in water, neutral in reaction and under normal conditions excreted as such through the urinary tract within eight to twelve hours to the extent of from 85 to 95 per cent. Iodism has never been observed. Its tolerance is exceedingly great. From about 45 to 65 per cent of the substance is normally excreted during the first two hours. For this reason, the urograms show their greatest intensity during this period.

The technic of administration is as follows: A 40 per cent solution is made up in doubly distilled water to a volume of 100 cc., filtered and then sterilized. Injection is done by means of several record hand syringes into the veins of the arm. The quantity administered is, for an adult, from 40 to 60 Gm. of the substance in a 40 per cent concentration. Younger persons receive proportionate doses. For children aged from 6 to 9 months the dose is 10 or 12 Gm. of the substance; up to 2 years, 14 Gm.; 4 years and up, 16 Gm.; 7 years and up, 20 Gm.; from 10 to 13 years, 25 Gm., and 13 years old and up, 30 Gm. It was found roentgenologically that the injection in adults of from 50 to 60 Gm. of substance yields the better shadows. If 60 Gm. of substance is used, the full quantity of the solution may be injected continuously, or half is injected first and then the other half ten or fifteen

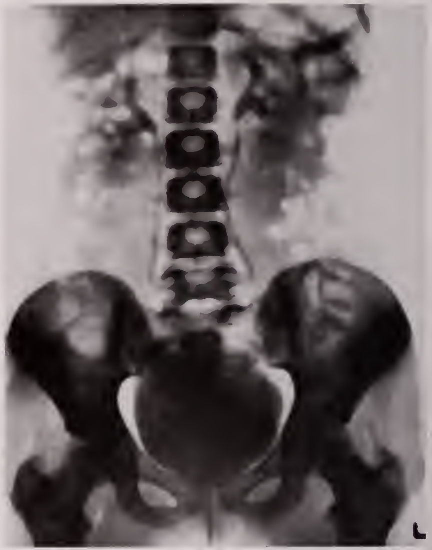

Fig. 1. — Normal urogram of an adult; 60 Gm. of substance injected.

Radiologist, The Mount Sinai Hospital, New York, NY; Consulting Radiologist, Montefiore Hospital, New York, NY.

*From the radiologic and urologic services of The Mount Sinai Hospital.

*The original article is abbreviated in *The Journal* by the omission of six illustrations. This version has all 12 figures, as depicted in the author's reprints.

*Read before the Section on Radiology at the Eighty-First Annual Session of the American Medical Association, Detroit, June 26, 1930.

Reprinted from *JAMA* 1930; 95:1409–1412, copyright 1930, with permission from the American Medical Association.

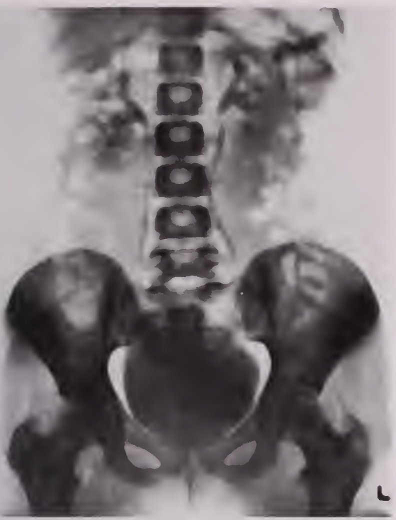

Fig. 2. Normal urogram of patient, aged 13½ years; 30 Gm. of substance injected.

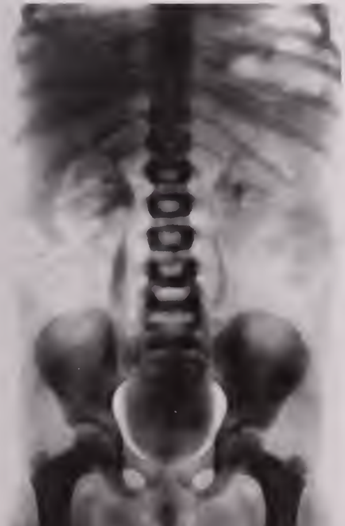

Fig. 3. Right-sided pyelo-ureteritis in girl, aged 5½ years; 16 Gm. of substance injected.

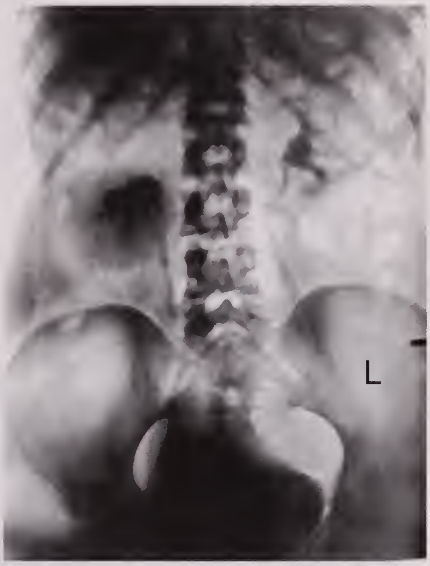

Fig. 4. Right nephropexy in woman, aged 31; 40 Gm. of substance injected; distortion due to operation; depression in left upper quadrant of bladder is due to the uterus.

minutes later. The shadows obtained then are nearly, though not quite, as dense as those by the retrograde or cystoscopic method. During the injection the patient has an evanescent sensation of thirst and warmth; occasionally in the injected arm pain is experienced during the injection. I have observed no other reaction.

The roentgen technic is that usually employed in urinary tract examinations: the Potter-Bucky diaphragm, a 14 by 17 film (occasionally a smaller size if only part of the tract is wanted), and compression by means of the rubber bag. The patient is kept on the table for at least one hour after the injection. The best roentgenologic results are obtained fifteen, thirty-five and sixty minutes after the last injection. After that period, good outlines are obtained only in cases of delayed renal function, combined with obstructive lesions. It is therefore important to have each film developed immediately in order to determine for how long a period the taking of roentgenograms should be continued. It may sometimes be necessary to take roentgenograms at one to three hour intervals until good shadows are obtained. Sometimes it is necessary to have the patient empty the bladder in order better to demonstrate the lower ends of the ureters.

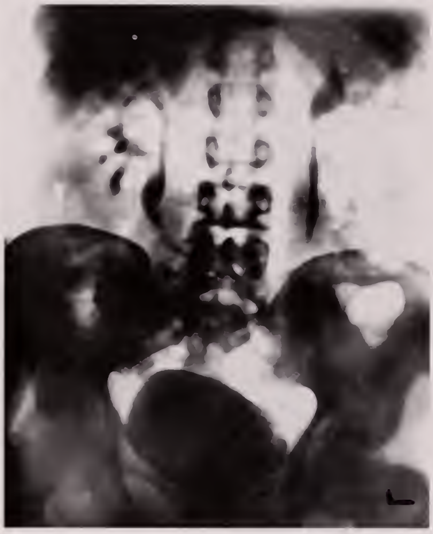

Fig. 5. Bifid right renal pelvis and forked ureter. A left retrograde pyelogram had been done three months before this intravenous urogram was performed. One week after the retrograde pyelogram was done, an intravenous urogram was performed which showed that the left kidney did not visualize at all, and the right kidney only slightly. This second intravenous urogram now shows that both kidneys are well visualized.

The intravenous method is indicated in all instances in which urography is desirable and is applicable in many more cases than the retrograde method, because the objections to instrumentation are eliminated. It has thus been possible to employ this method in children as young as 6 months and in adults with large prostates, cardiac disease or other contraindications.

Contraindications to the use of the intravenous method would be actual or latent uremia in which, as a result of the poor concentrating power of the kidney, meager or no anatomic information could be obtained. For functional data, much simpler and less expensive methods, such as the blood urea determination, the phenolsulphonphthalein, indigo carmine, and the dilution and concentration tests can be applied. In addition, the procedure might prove dangerous. Therefore, it is strongly advocated by Swick that patients about to be subjected to the intravenous procedure should have at least a blood urea, phenolsulphonphthalein and concentration tests performed. The intravenous method, however, does not eliminate the retrograde or cystoscopic method; this is especially true in cases in which kidney function is impaired and therefore the iodine concentration is so poor that the tract is not sufficiently visualized. Here the retrograde method has to be resorted to in order to obtain an anatomic outline of tile renal pelvis and ureter. The bladder will generally be shown well, unless both kidneys are below par. The faintest shadows are obtained with poorly functioning kidneys, the densest when obstruction is present. The roentgenographic contrast is heightened by means of the compression bag, which should be kept on for from five to ten minutes prior to and during the taking of the roentgenograms. One or more after each of these might also be taken without compression.

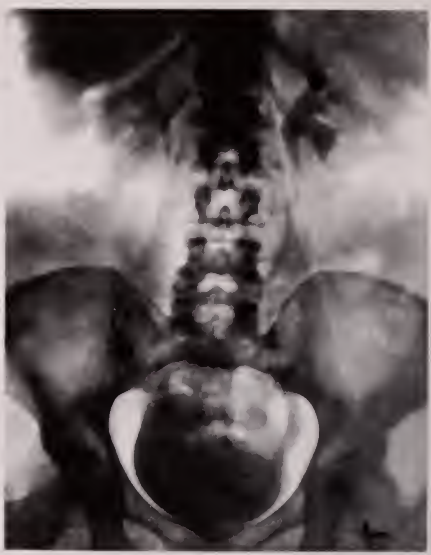

Fig. 6. Papillary carcinoma of urinary bladder extending from the left orifice to the internal sphincter, according to cystoscopic diagnosis, in woman, aged 62; 50 Gm. of substance injected. The left ureteral orifice cannot be seen. There was no indigo carmine excretion from left side; good blue from right. Intravenous pyelogram shows dilatation of left urinary tract, especially of juxtavesical and intravesical portions of the ureter. The denser shadow on the left than on the right normal side is due to partial obstruction at the left ureteral orifice.

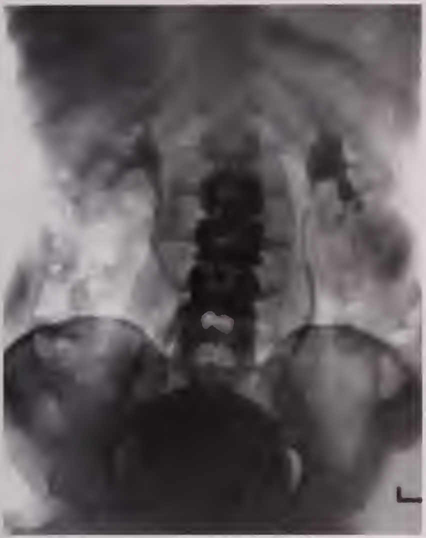

Fig. 7. Enlargement of the pelvis and calices of left kidney, but only slight distortion of one of the lower calices, in a man, aged 38; 60 Gm. injected. At operation a clear cell carcinoma was found.

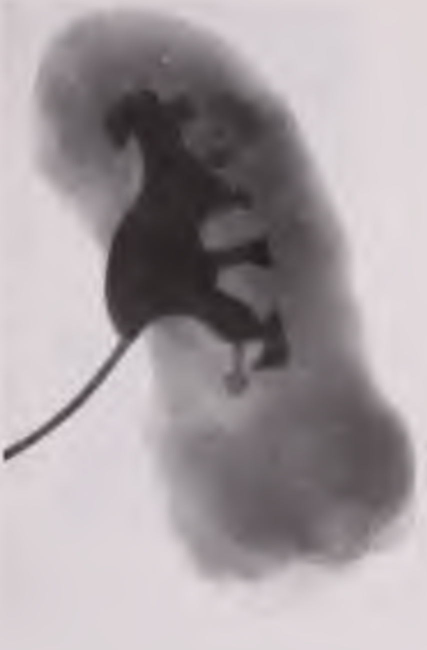

Fig. 8. Specimen of left kidney of the patient shown in Fig. 7.

The advantages of the intravenous method are manifold. It intensifies the kidney shadows, frequently bringing out irregularities in outline. Instrumentation is avoided which even under favorable circumstances is to say the least, very unpleasant and which, as will be seen from some of the illustrations, seems to cause a temporary inhibition of function of the kidney subjected to it. The entire urinary tract, including the bladder, is shown at one application of the method. With the cystoscopic method it has generally been found necessary to inject each side at separate sessions so as to avoid the severe reactions that frequently followed bilateral pyelography performed at one session. For the same reason the intravenous method is safer in case of solitary kidney. Anomalies in the urinary tract, such as double ureters, are revealed in some cases in which the cystoscopic method failed for technical reasons. It is not subject to failure in stricture of the ureter and is the only useful method in the study of the result of transplantation of ureters. It eliminates the artefacts which not infrequently complicate the other method and sometimes makes one hesitate to designate a transparency within the opaque material as a calculus rather than an air bubble or to say that a defective calix is due to a pathologic lesion and not to poor injection technic, especially when the urologist happened to be one of limited experience.

An added advantage of this method is that it demonstrates not only the anatomy of the urinary tract but also its function. The roentgenographic determination of function is, however, not sufficient in itself; according to Swick it should be supplemented by the quantitative determination of the excreted substance, which can be recovered from the urine. It will undoubtedly also give information regarding peristalsis of the ureters and the physiology of the pelvis and calices. In some cases of renal calculus, spasm of the calices was shown, probably as a reaction to the presence of the foreign body. In others in which the retrograde method preceded the intravenous, temporary nonvisualization on that side was present. It is important, therefore, to remember that the mere nonvisualization at a given examination does not necessarily denote permanent renal damage and

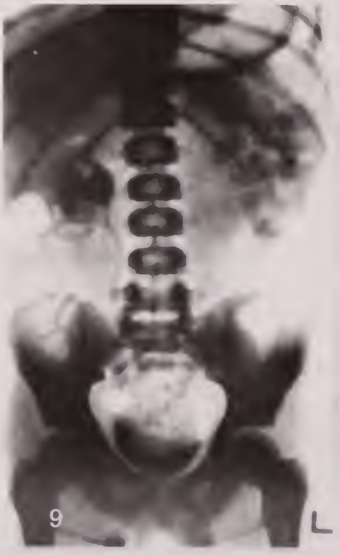

Fig. 9. Enlarged right renal pelvis, shown by intravenous urography, in a boy, aged 12; 30 Gm. of substance injected. The boy had pus in the urine when 1 year of age and urinary symptoms ever since. For seven years he had pain in the left upper quadrant and left loin. On the left side, the calices, which filled first, as they do in all hydronephrosis, were enormously enlarged.

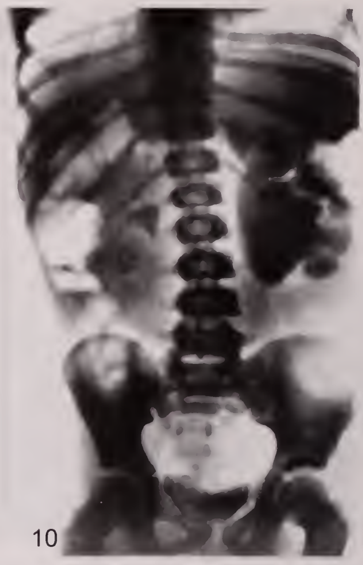

Fig. 10. Later film of same case as Fig. 9, showing the pelvis to be of enormous size. The ureter was not seen at all. Left nephrectomy disclosed an infected hydronephrosis caused by narrowing of the ureteropelvic junction, probably congenital in origin.

therefore it is wiser to use the term functional inhibition.

One Hundred East Ninety-Fourth Street.

Abstract of Discussion

Prof. Leopold Lichtwitz, Altona-Elbe, Germany: Pyelography by way of excretion is an old desire. Dr. Rowntree was the first to attempt the visualization of the urinary tract by means of sodium iodide. Professor Binz of Berlin, who for a long time was greatly interested in chemotherapy, invented and prepared with his collaborators the group of selectans. Selectan and selectan neutral were sent by him to the clinic at Altona with the idea of attempting to influence coccus infections. In order to attempt treating infections of the kidney pelvis and gallbladder, we studied the output by the kidney and liver. We obtained evidence that the preparations did not cause iodism. The fact that these selectans are iodine-containing, excretable by the kidneys and liver and cause no iodism, which had been the greatest obstacle in the earlier attempt, naturally led to the idea of testing them for the widely desired intravenous pyelography. Surely the invention of Professor Binz is the one leg of the new method. The second basis is the work of Dr. Swick. Important as is the existence of preparations, they become valuable only when the right person takes them for a special purpose. This is made clear by the fact that the preparations of Professor Binz were tested for the same purpose before Dr. Swick began his studies (without his knowledge) by a man of great experience in research work — without sufficient results. Between the important work of chemical preparation and final success, there came the hard work of a clever and energetic man, one with the deepest devotion to and greatest passion for research work. Therefore, we appreciate the work of both Professor Binz and Dr. Swick, and as this work is based on the invention of a famous German chemist and the investigations of a young American working in Germany, it may be considered as another hopeful symptom of scientific cooperation and friendship between our two countries.

Prof. Arthur Binz, Berlin, Germany: It was my idea in 1921 to attach arsenic, or other elements such as iodine, to heterocyclic nuclei, such as those of the alkaloid group, and possibly thereby intensify therapeutic efficiency in the treatment of syphilis. My assistant, Dr. Räth, and I chose the simplest heterocyclic nucleus, the pyridine, and transformed it into about 700 new arsenic and iodine compounds. Expecting them to be very toxic, we were much surprised to find several of an unheard of tolerability when compared with the known arsenic and iodine compounds. This new biochemical principle, which we ascertained in animal experiments, caused me finally to select sodium-2-oxo-5-iodo-pyridine-N-acetate ("Uroselectan") for intravenous urography. This new relationship between chemical structure and biologic action we published in the *Zeitschrift für angewandte Chemie*. Sodium-2-oxo-5-iodo-pyridine-N-acetate, in its present form, was made in 1927, long before Dr. Swick came to Germany. Its selection by me for the purpose of intravenous urography was not due to suggestions of Dr. Swick but was in answer to clinical principles which had been agreed on by Professor von Lichtenberg and me, before Professor von Lichtenberg's trip to America last year. Concerning priority, Hryntschak of Vienna in 1927 was the first to investigate selectan compounds for intravenous urography, including what is now known as sodium-2-oxo-5-iodo-pyridine-N-acetate. Hryntschak obtained but partial success. Professor Lichtwitz of Altona in 1929 in his investigation of the treatment of human infections by selectan neutral, which I had sent him, observed that this compound had another effect which concerned intravenous pyelography. But all these results were clinically negligible. After working with selectan neutral and other selectan compounds, in Professor von Lichtenberg's clinic, and obtaining disappointing results, final success was achieved when I selected sodium-2-oxo-5-iodo-pyridine-N-acetate for use. It was given by me to Dr. Swick, who had been appointed by Professor von Lichtenberg to try out the compounds that I would give him.

Dr. Moses Swick, New York: When I began my studies, as Professor Lichtwitz has pointed out, a substance synthesized by Professors Binz and Räth, having the formula m-

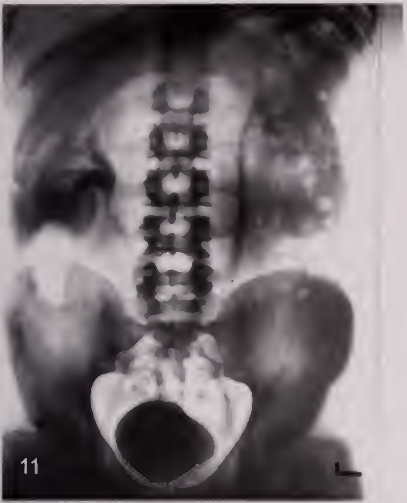

Fig. 11. Deformity of left renal pelvis and calices, a cavity, absence of the middle calix, and a straight rigid ureter suggestive of tuberculosis, in a man aged 32; 60 Gm. of substance injected.

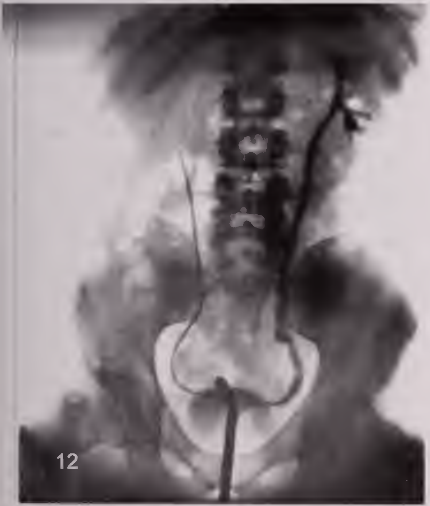

Fig. 12. Same case (as Fig. 11). Left retrograde pyelogram two days later presented same appearance but did not visualize the cavity as clearly. Subsequent nephrectomy disclosed an isolated tuberculous cavity in the kidney as shown in Fig. 11.

methyl-5-iodo-pyridon ("Selectan Neutral") was being tested for coccus infections at his clinic in Altona, Germany. Studies on its excretion, and its iodine content, led to the idea of applying it for roentgenologic purposes. The encouraging results pointed to the possibilities of further development. Following a dose of 6 Gm. (one third of the calculated maximal dose), certain disturbing symptoms resulted. Some were headache, nausea, vomiting and general discomfort. Of particular interest was the occurrence of transient diplopia in two cases. This suggested the possibility of the methyl radical being the toxic factor. My experience with this substance brought out the need for a modification, possessing better tolerance, greater solubility, and a higher iodine content, so that a larger dose could be administered and a higher concentration of the excreted iodine component be obtained. This work had been carried out at the clinic of Professor Lichtwitz for seven months before conferences were held with Professor Binz. The full data concerning these conferences and other matters here discussed will be presented by me tomorrow before the Section on Urology. As a result of my first presentation of the needs to Professor Binz, he furnished me with a compound, which, because of its insolubility, had to be administered by mouth and gave no results. At the second conference, in which Professor Lichtwitz participated, the whole ground was gone over again. Professor Binz felt confident that our needs could be fulfilled. Thereafter I continued the investigations in the clinic of Professor von Lichtenberg. There again I tested "Selectan Neutral," the second substance, and a third furnished by Professor Binz, which also had to be given by mouth and was unsuccessful. Finally, Professor Binz gave me a substance of the selectan group, which had a sodium acetate radical substituted for the methyl (sodium-2-oxo-5-iodo-pyridine-N-acetate). This compound fulfilled the needs, and satisfactory urograms could now be obtained. Professor von Lichtenberg, who was in the United States at the time, was promptly informed of the results. These were reported by me in detail at the Urologic Congress in Munich in September, 1929. I am not a chemist but have interested myself along the chemical lines required by the theoretical side of my problem and the chemical examinations needed in the course of the clinical investigations.

Dr. Theodore Sokow, Kenosha, Wis.: The use of this new method necessitates changing one's conception in explaining and diagnosing roentgenograms. With the cystoscopic method, a forcibly dilated kidney pelvis is obtained, not corresponding to the anatomic conditions. With the intravenous method, the physiologic dynamic conditions of the kidney and ureters are observed. That explains why pictures taken at the moment of the kidney contraction may show the pelvis very small and the calices not at all. Only in the diastole is a perfect picture obtained. Certain technical procedures may improve the results, as elevation of the pelvis of the patient and compression of the region of the lower ureters. In one of the latest articles, Dr. Hryntschak of Vienna is recommending the use of solution of pituitary to increase the concentration of the dye in the kidney and atropine to delay the excretion of the dye. It seems worthwhile to try these and other drugs for the same purpose. In my experience, sodium-2-oxo-5-iodo-pyridine-N-acetate has given very good results and few after-effects. About two months ago, at the annual convention of the German Roentgen Society in Berlin, different authors mentioned a new product, produced by another chemical concern in Germany. I was able to secure lately a small amount of this chemical, and used it in different cases with very satisfying results.

Dr. L.T. Le Wald, New York: Dr. Jaches has brought out two or three uses that seem to me very important. As I have had one case of implantation of both ureters into the sigmoid, similar to his case, and as I know of several cases at the Mayo Clinic, I would be interested to learn whether the rest of these cases could be examined and see whether dilatation of the ureters has occurred in the other cases in which there was exstrophy of the bladder. The second point relates to the possibility of misinterpretation, because one kidney didn't show function temporarily which might lead one into error. Dr. Jaches, however, has emphasized the fact that either repeating the test or roentgenographing the patient at a little later time shows that the kidney did function, thus avoiding erroneously diagnosing a single kidney because of this possibility of spasm interrupting the secretion. And then in case of horseshoe kidney, I think it is exceedingly valuable. Occasionally in a thin subject, at least in one case, I was able to see the shadow of the kidney going across the median line, but as a rule one would be in doubt in a case of that sort. In Dr. Jaches' case, the shadow was certainly very conclusive after the use of sodium-2-oxo-5-iodo-pyridine-N-acetate. I would like to ask Dr. Jaches if any alarming reactions have occurred. A urologist in New York told me that in his first case in which the injection was given through rubber tubing he had had some reaction and he did not give more than half the dose and then desisted from finishing the examination, saying that the patient had some dizziness and collapse, and he didn't feel safe in going on. I wish Dr. Jaches would say a word or two more about technic.

Dr. B. R. Kirklin, Rochester, Minn.: You might be interested to know of a little Scotch trick that we have employed at the Mayo Clinic. Dr. Braasch and his associates have been collecting the urine of the patients after they have received sodium-2-oxo-5-iodo-pyridine-N-acetate and sending it to the chemist, who has been able to recover approximately 65 per cent of the amount originally injected. I am informed by the chemist that the substance recovered in this way is a purer product than the original drug.

Dr. Leopold Jaches, New York: In 122 cases there have been no unpleasant reactions. What was the cause of the reaction in the case quoted by Dr. Le Wald, I do not know. It may be that this patient was an unsuitable subject. I suggest that this case be reported with all clinical data, so that more can be learned about all possible contraindications than is known today. I am glad to hear from Dr. Kirklin that at the Mayo Clinic the material was used over again. Dr. Swick has proposed the same thing to me but as yet I have not followed his suggestion. I made up my mind to keep out of the controversy regarding the origin of this matter. I would like, however, to say in connection with what has been stated concerning Dr. Hryntschak, that a real practical success did not result from his studies. As Dr. Swick is much more familiar with this phase of the subject, he should be permitted to discuss it for me.

Dr. Moses Swick, New York: At the Urologic Congress, in Munich in 1929, where I presented my paper, Dr. Hryntschak was present. He did not discuss the subject but in his article which appeared at that time in the *Zeitschrift für Urologie* in 1929, he said on page 904 that although he had succeeded two and one-half years before in obtaining useful pyelograms in a few cases, the method had by no means met the conditions set forth by him. He, however, expressed the hope of accomplishing his aims by continued investigations. I might add that he gave neither the name nor the chemical formula of any of the substances employed, but he mentioned three of them by number as 12, 27 and 48.

Dr. Leopold Jaches

ANNOUNCEMENT OF 2002 AWARDS

The Mount Sinai Journal of Medicine offers several prizes for manuscripts published in *The Journal* during the previous year, and judged by our awards committee to be outstanding contributions to the medical literature. The committee's task was formidable this year because of the especially high quality of the papers nominated, but I believe that it has chosen wisely and well. The efforts of the members are much appreciated.

The Joseph Globus Award, established in honor of the first and long-time editor of *The Journal*, is for the best overall paper on any medical topic. The award goes to Richard N. Bergman, Ph.D., for his paper "Pathogenesis and Prediction of Diabetes Mellitus: Lessons from Integrative Physiology," volume 69 (5), pp. 280–290.

The Ralph Colp Award, in honor of the memory of a distinguished chief of surgery at The Mount Sinai Hospital, for the best paper on a surgical topic, goes to Sian Jones, M.D., Clyde B. Schechter, M.D., Cheryl Smith, M.D., and David N. Rose, M.D., for their paper "Is HIV Infection a Risk Factor for Complications of Surgery?" volume 69 (5), pp. 329–333.

The House Staff Award, for the best paper principally prepared and written by one or more members of the Mount Sinai House Staff, goes to Avi Fischer, M.D., Rajiv Verma, M.D., Joseph A. Gomes, M.D., and Davendra Mehta, M.D., Ph.D., for their paper "Ventricular Arrhythmia: Role of the Implantable Cardioverter Defibrillator and Radiofrequency Ablation in Addition to Drugs," volume 69 (4), pp. 197–207.

The Student Award, for the best paper principally prepared and written by a student, goes to Joe F. Lau, Ph.D., for his paper "Mechanisms of Type I Interferon Cell Signaling and STAT-Mediated Transcriptional Responses," with Curt M. Horvath, Ph.D., volume 69 (3), pp. 156–168.

On behalf of the Editorial Staff, Dr. Leslie A. Kuhn, Associate Editor, and I are delighted to recognize the outstanding scholarship and contributions of our 2002 awardees to medicine in general, and to *The Mount Sinai Journal of Medicine* in particular.

Sherman Kupfer, M.D.
Editor-in-Chief

INFORMATION FOR AUTHORS

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of The Mount Sinai Hospital*, is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts*, and other major databases. The abstract and full text of each published article is posted on *The Journal's* web site <www.mssm.edu/msjournal> where it can be accessed by the reader. *The Journal*'s web site is linked to that of the National Library of Medicine. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcomed.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@mssm.edu; world wide web: www.mssm.edu/msjournal.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and either (3) the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in *The Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal*'s office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations and a disk (see below). **Manuscripts must be computer generated, double spaced throughout (including references, legends, and tables)**, on one side of $8^1/_2 \times 11$ inch white bond paper with **one inch** margins. The title page must be entirely separate and should designate the location(s) where the work was done, and the name and address of the corresponding author. The abstract page(s) should be numbered sequentially as i, ii, iii, etc. A separate page should be used for each table. The legends, in numerical sequence, should be typed together on one or more pages (if needed). A separate page, or pages, should list the references in the sequential order they are cited for the first time in the narrative text. A disk should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted (Windows, MAC), and the software used (WordPerfect, MS Word, etc.). PC format is preferred, but a high-density, formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or WordPerfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page(s) or in legends. Define all abbreviations on first use in the body of the manuscript. All abbreviations used in a table must be defined at the bottom of the table.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher, giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If the manuscript deals with specific patients for whom identifiers (as defined by HIPAA) are provided, the consent of each patient for the release of information must accompany submission of the manuscript. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office (or its equivalent) which supervises such work.

Title Page. This page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, and middle initial(s), if any, and not more than two academic degrees; (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and telephone and FAX numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom an offprint is to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and (9) **a running head of fewer than 40 letter spaces.** At the bottom of the title page, **list 3 to 10 key words or phrases** to facilitate computer searches in accord with medical subject headings from *Index Medicus.* If more than one sheet is needed, label the supplemental sheet as "Title Page (cont.)."

Abstract. All articles must include an abstract of not more than 400 words. The pages containing the abstract should be numbered sequentially as i, ii, iii, etc. This abstract will be published in *The Journal* with the article. Enough detail should be provided in the abstract so that it will be sufficiently informative to stand alone when placed on *The Journal*'s web page (prior to publication of the entire article in *The Journal*). Abstracts should be double spaced. Abstracts for manuscripts specifically describing original clinical and/or laboratory research should be structured in four paragraphs:

Background: what problem(s) was (were) addressed;
Methods: how the study was performed;
Results: the most significant results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page and also after the abstract to facilitate computer searches. **Repeat at the end of the abstract the same key words which are listed on the title page.**

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning, in conformity with the style used by *The Journal.* Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high-contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of $3^{1}/_{8}$ inches. **The type of stain and power of magnification (e.g., 10X, 40X, 100X, etc.) must be indicated in the relevant legend**. Electron photomicrographs should have internal scale markers. On the back of each print and photograph, affix a gum label on which the number of the figure has been written to correspond to its identification in the text, as well as the title of the manuscript, first author's last name, and the word "top" and an arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial features should be masked to prevent identification of the subject unless they include details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

The Journal does not publish color images unless the author is willing to pay for the additional expense involved. Should the author wish to consider publishing images in color, 3 copies of each color print must be included with the manuscript. If the manuscript is accepted, the author will be informed of the extra cost involved. A check for this amount must be received prior to publication. If, however, the author wishes to have color images appear **only in *The Journal's* web page version** of the article, one copy of each color print (rather than 3) along with the 3 black and white glossy prints must be submitted with the manuscript. The web page version of the manuscript will not involve additional expense to the author.

Legends. Legends should not duplicate the text. They should appear together in numerical order, typed double spaced, on one or more pages following the text. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle," etc.) or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Footnotes. Except as noted above in the section "Units of Measurement," the use of footnotes is to be avoided. All relevant information should be incorporated directly into the narrative text, and appropriately cited as noted below in the section "References."

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (**TABLE 1**, etc., in bold type) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text, and type the title, *in italics*, on a separate line below the table's number. Identify all abbreviations and/or symbols used in the table in a footnote at the bottom of the table.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., **Cytomegalovirus (1), steroids (2, 3), and recreational drugs (4-6) have all been implicated (7).** Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus*. The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled "References" are illustrated in the version of "Uniform Requirements" published in *The New England Journal of Medicine* referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style shown in the examples below. The list of references should not be formatted as "Endnotes."

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309–315.

3. Couser WG. Glomerular diseases. In: Stein J, editor. Internal medicine. 2nd ed. Boston: Little Brown; 1987. pp. 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then "et al."

A citation to an article that has not been published in print (journal, book) and that has been obtained by accessing a website must include, in addition to the names of the authors and the title of the article, the precise uniform resource locator (URL) address at which the article can be found and accessed. This address can usually be found as a long stream of characters and numbers after the prefix "http://www.........."

References to unpublished data (unless the information is in press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission.

If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.

Proofs. A revised, copy-edited manuscript will be sent to the corresponding author as soon as it is available, for necessary corrections only. **Stylistic changes should not be made**. All corrections should be made on this copy, which must be returned to the *Journal* office as soon as possible (see "Communications" above). This corrected, revised, edited version of the manuscript will be sent to the printer for typesetting directly from a disk. "Galleys" will not be sent to the corresponding author for review.

Offprint Orders. A "Request for Offprints" form will be sent to the corresponding author. If offprints are desired, the form must be returned to the editorial office. When the article is scheduled for publication, an "Offprint Order Form" and "Shipping Label" will be sent to the corresponding author. These must be completed and returned with a check for the exact amount in US dollars made out to *The Mount Sinai Journal of Medicine*. Please indicate on the check the last name of the first author, and the title of the article. If, for one reason or another, an "Offprint Order Form" and "Shipping Label" are not received by the corresponding author, they may be obtained directly from the *Journal* office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the total number of printed pages and whether covers are desired. The cost of delivery must be added to the cost of the offprints. Information on cost of other than routine delivery can be obtained from the *Journal* office.

09/200

Required Form for Authors

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal*.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

4. US Federal Employees

I was an employee of the US government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

09/2002

LEVY LIBRARY, MT SINAI SCHOOL OF MEDICINE
3 4805 0792902 5

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Forthcoming: Grand Rounds

A Review of Heart Failure Treatment
Gordon H. Guyatt and P.J. Devereaux
McMaster University
Hamilton, Ontario, Canada

Renal Artery Disease: Diagnosis and Management
Jeffrey W. Olin
Mount Sinai School of Medicine

The Electrocardiogram as a Predictor of Left Ventricular Systolic Function: Correlation with Gated SPECT Imaging
Milena J. Henzlova and Lori B. Crof
Mount Sinai School of Medicine

Cardiovascular Disease in Women
W. Lane Duvall
Mount Sinai School of Medicine

Theme Issues

Ethics 2001 — Medicine, Money and Morals
Rosamond Rhodes and Daniel A. Moros, Editors

Minimally Invasive Vascular Surgery: The Evolution of Endovascular Therap
Michael L. Marin, Larry Hollier, and Valentin Fuster, Editors

Available now:

Methadone Symposium – Part 1:2000
Volume 67: Numbers 5 & 6. 125 pages, $40.00
Methadone Symposium – Part 2:2001
Volume 68: Number 1. 78 pages, $25.00

Issues in Medical Ethics — Understandin
Professionalism and Its Implications for
Medical Education
Volume 69: Number 6. 71 pages, $25.00

Visit our web page — http://www.mssm.edu/msjournal

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 70 NUMBER 5 OCTOBER 2003

CONTENTS

COMMENCEMENT ADDRESS — 2003

Physicians and Scientists for Your Grandchildren *Arthur H. Aufses, Jr.* 289

GRAND ROUNDS

Cardiovascular Disease in Women *W. Lane Duvall* 293

The Electrocardiogram as a Predictor of Left Ventricular Systolic Function: Correlation with Gated SPECT Imaging *Milena J. Henzlova and Lori B. Croft* 306

GENERAL ARTICLES

Cardiothoracic Surgery at The Mount Sinai Hospital *Robert S. Litwak* 310

The History of Thoracic Surgery at Mount Sinai *Paul A. Kirschner* 326

Minimally Invasive Endocrine Surgery *Michael D. Addis and William B. Inabnet* 333

Emergency Prophylaxis Following Needle-Stick Injuries and Sexual Exposures: Results from a Survey Comparing New York Emergency Department Practitioners with their National Colleagues *Roland C. Merchant and Reza Keshavarz* 338

Controversies in Differentiating Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome *Neelam T. Shah and Jacob H. Rand* 344

EDITOR'S NOTE 352

CLASSICS IN MEDICINE

An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries: An Undescribed Disease* *Eli Moschcowitz* 353

Information for Authors i

SAINT BARNABAS HEALTH CARE SYSTEM

LIBERTY HEALTHCARE SYSTEM, INC.

Veterans Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by the Mount Sinai Medical Center of New York and has t
following affiliates: Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Queens, NY;
Queens Hospital Center, Queens, NY; Saint Barnabas Health Care System,
Livingston, NJ; Newark Beth Israel Medical Center, Newark, NJ; Liberty
HealthCare System, Inc., Jersey City, NJ.

Editor-in-Chief

Sherman Kupfer, M.D.

Associate Editors

Harriet S. Gilbert, M.D.
Leslie A. Kuhn, M.D.
Philip S. Ledereich, M.D.

Administrative Assistant

Ron Stein

Assistant Editor for Housestaff

Leora Horwitz, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

Scott H. Barnett, M.D.
J. Hugh Baron, D.M.
David H. Bechhofer, Ph.D.
Constantin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Donald Brief, M.D.
Daniel Buchbinder, D.M.D, M.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., M.P.H., M.P.P.
William H. Constad, M.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
James N. Gladstone M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Jack Hirschowitz, M.B., Ch.B.
Fred M. Jacobs, M.D., J.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M. Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkovitz, M.D.
Dana M. Lewis, M.L.S.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Myron Miller, M.D.
Richard Panush, M.D.
Barbara E. C. Paris, M.D.
Jerome G. Porush, M.D.
Georges R. Ramalanjaona, M.D., D.Sc.
Veronica A. Ravnikar, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Tibor Rohacs, M.D.
Gregory J. Rokosz, D.O., J.D.
Joshua Rosenblatt, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Harry Schanzer, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Janet B. Serle, M.D.
Phyllis Shaw, Ph.D.
Scott H. Sicherer, M.D.
Barry D. Stimmel, M.D.
Nelson N. Stone, M.D.
Max Sung, M.D.
Jules A. Titelbaum, M.D.
Thomas A. Ullman, M.D.
Richard P. Wedeen, M.D.
Klaudiusz R. Weiss, Ph.D.

Editorial Board

Barry S. Coller, M.D.
Kenneth L. Davis, M.D.
Panayotis G. Katsoyannis, Ph.D.
Jack G. Rabinowitz, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, Septe
October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-
Subscription price: individuals (U.S. and Canada), $79 per year; libraries and institutions (U.S. and Canada), $121 per year; individuals (o
U.S. and Canada), $105 per year; libraries and institutions (outside U.S. and Canada), $147 per year. The charge per copy of a single nu
issue is $25, for a two-number issue is $50. New subscriptions begin with the first issue of the calendar year. Send notice of change of ac
60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send ac
changes to *The Mount Sinai Journal of Medicine*, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212
6108. Fax (212) 722-6386. e-mail: msjournal@mssm.edu; web page: www.mssm.edu/msjournal. Copyright 2003.

DISCLAIMER: The statements and opinions expressed in *The Journal* by authors and contributors are solely their own and not those of The Moun
Medical Center or *The Mount Sinai Journal of Medicine* All advertisements are expected to conform to ethical standards, and their appearance does no
endorsement or approval by The Mount Sinai Medical Center and/or *The Mount Sinai Journal of Medicine* of the products with respect to effectiveness, qu
safety The Mount Sinai Medical Center and *The Mount Sinai Journal of Medicine* do not hold themselves responsible for statements made by the aut
contributors and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisement

COPYRIGHT: Material printed in *The Journal* is protected by copyright. In accord with U.S. Copyright law, no part of *The Journal* may be reproduced,
displayed or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior w
permission to do so. Permission should be requested from The Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 10
One East 100th Street New York NY 10029-6574.

Commencement Address—2003

Physicians and Scientists for Your Grandchildren

Arthur H. Aufses, Jr., M.D.

Dean Davis, Mr. May, Dr. Graybiel, Dr. Fuchs, Dean Kase, fellow faculty, all the graduates and their families, my family, friends and guests.

I thank you all for the singular honor that you have bestowed upon me today. In one's lifetime, there is one moment that can be considered to be the capstone of one's career. I can truly say that today is the pinnacle of my own career.

I especially want to thank Dean Kase for having invited me to give this address. There is no one in Avery Fisher Hall more elated than I to see Dr. Kase receive the honorary degree of Doctor of Humane Letters. Nate and I have known each other since 1955, when he was an intern and I was the chief resident in surgery. Everyone associated with Mount Sinai knows what a great chairman of Obstetrics, Gynecology and Reproductive Sciences he was from 1981 – 1985 and what a remarkable dean he was from 1985 – 1997, and how he stepped into the breach as interim chief executive officer and interim dean from 2001 until just a few months ago, and held us together. There are few here today, however, who know how instrumental he was in the formation of this medical school more than 40 years ago. It is a story that bears telling today.

In 1961, the leadership of The Mount Sinai Hospital invited two of the leading medical educators in America to visit the hospital and advise them on whether to proceed with the development of a medical school. A number of then-current research projects were presented to the visitors, including a presentation by Dr. Kase, who was still a resident in Obstetrics and Gynecology but was spending time in research. These presentations, and especially the one by Dr. Kase, so impressed the visitors that they enthusiastically recommended proceeding with the formation of the school. And so Dr. Kase deserves great credit not only for what he has done for the school these past 20+ years, but also for his role in its creation. We are all indebted to Dean Nathan Kase, and I for one salute you.

There are so many other people to whom I owe a personal "thank you" that to name them all would use up my allotted time. There is, however, one person whose love, help, support and encouragement has enabled me to devote so much of my life to Mount Sinai, and who I wish to acknowledge and with whom I share this honor. We have stood side by side for more than fifty- five years. She is a beautiful, great and elegant lady, a wonderful wife, mother, mother-in-law and grandmother. Ladies and gentlemen — Harriet Aufses.

Today, as we honor our graduates and our honorary degree recipients, we celebrate the 34th commencement exercise of the Mount Sinai School of Medicine. This is the 34th commencement address. Previous speakers have included senators and congressmen; leaders in science, ethics and medicine; leaders of great causes; the clergy; and a television personality. For example, in 1973, at Mount Sinai's fourth commencement, the writer and scientist Isaac Asimov was the commencement speaker. Our current chief executive officer and dean, Dr. Kenneth Davis, was a member of that graduating class. Although I am going to ask you, the graduates, some questions in just a moment, I will not ask the dean if he remembers what Dr. Asimov said on that occasion.

There are two adages that are applicable to commencement addresses. The first is: "To be

---

Professor of Surgery, Department of Surgery and Professor of Health Policy, Department of Health Policy, Mount Sinai School of Medicine, One East 100th Street, New York, NY.

Address all correspondence to Arthur H. Aufses, M.D., Department of Health Policy, Box 1077, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Accepted for publication June 2003.

seen one must stand up, to be heard one must speak out, and to be appreciated one must sit down." The other is: "Be brief, be brilliant, be gone." I will try to adhere to these statements. Commencement addresses are supposed to present uplifting thoughts for the graduates. Unfortunately, however, they are almost always quickly forgotten. One obvious reason for this is that all of you want to get on with the business at hand. After all, this speaker is one of the few remaining hurdles standing between you and your degrees. I believe that a more important reason however, is the nature of this interaction. I am standing here, immobile, without my usual Powerpoint slides, while you are sitting passively in your seats wondering how long this address will go on. Learning theory says that in order for a lecture to have any impact, the audience must participate and take an active role in the process. And so, I hope to be able to engage you in a way that will, at least, have you remember my main premise.

First, I would ask the graduates to stand and look around them and consider this venue. Avery Fisher Hall has 2,738 seats. Almost every one of those seats is occupied. On the stage In front of you and immediately behind you are the faculty whose teaching and mentoring has enabled you to reach this milestone in your careers. But more than 2,000 of the seats are occupied by your families and your friends. Without their love and support you would not be here today. And so I would ask you to join with me in a salute to all of those who join you here today to help celebrate your graduation.

It has been said that no one ever forgets where they were and what they were doing at critical times in our history, on days such as Pearl Harbor, the day President Kennedy was assassinated, and September 11, 2001. You will certainly never forget today, May 9, 2003, and neither will I. But let's give the graduates a quiz and see how they do with a few other important dates in their own lives. I won't call on anyone by name, but who can tell me what they were doing on August 10, 1999? It was your first day in a Mount Sinai classroom. Does anyone remember who the first speaker was? It was Dr. Hillel Swiller. Does anyone remember the wonderful and apt mnemonic device that he provided you with to help cope with the stresses of medical school? It was R-A-F-T . . . the R standing for Relationships, the A for Autonomy, the F for Fulfillment, and the T for Take good care of yourself. If the RAFT helped you during medical school, it will be even more important in the days, months and years to come.

After Dr. Swiller's opening comments, I participated in a panel discussion with you and told a story. I related that my father, who had come to Mount Sinai in 1921 as an intern and remained on the staff for his entire career, said after retirement that his 50 years in medicine were the greatest in the history of the profession. My comment that day in 1999 was that after 50 years I could say the same thing, and after 50 years in medicine all of you will probably make the same statement. It is less than four years since your first day, but I think you would agree that the progress in genomics and gene therapy, as examples, starts your first half-century in medicine on a great journey. As an arch Mount Sinai chauvinist, I hasten to add that a great deal of that new knowledge has emanated from your school.

I have entitled this address "Physicians and Scientists for Your Grandchildren" and would like to focus on the role that you will play in producing those physicians and scientists. Although when I look at all of you, much of my concern regarding the availability of physicians and scientists for subsequent generations disappears, I always worry about the possibility that some day, the best and brightest of our young people will shun medicine and science. Medicine and science have been under siege for at least two decades, and even though applications to medical schools are up again after many years of steady decline, we cannot become complacent. All of you took a bold step in choosing to enter medicine and science. You, our graduates, are the individuals who must take the responsibility for recruiting and then teaching the next generation of physicians and scientists.

Last year, in his commencement address to the Class of 2002, Dr. Barry Coller spoke on "Science and Humanism: The Twin Pillars of Medicine" (1). Medical schools are based upon a tripod — the legs of the tripod representing patient care, teaching, and research. We can equate Dr. Coller's science and humanism with research and patient care. Today I would like to center my remarks around the third leg of that tripod — teaching, the teaching that all of you are going to be doing throughout your careers and that will be critical to the training of your successors. The verb "teach" has several meanings pertinent to my comments. In addition to "instruct" and to "impart knowledge," it also means to "show, guide, and/or direct." Teaching is also a form of mentoring.

Lest any of you think that you are not teachers, I would submit that all of you have been teaching since you have been at Mount Sinai; most of you probably started much earlier. This is a wonderful, collegial class that has worked together from day one. You have taught each other, you have taught the students in the classes behind you, you have taught college and high school students, you have taught us, the faculty, and in the future you are going to be teaching your successors. But most of all, you have taught patients and their families. And it is critical that you do not forget that role in your interactions with your patients. You will be teaching them about health in general and their various illnesses in particular. And as lifelong learners you will always live up to the adage "teach thyself." One of the definitions of "teach" noted earlier is to "guide." You are also going to have to guide your patients along the many paths that their illnesses take them; in many instances it will not be easy for either them or you.

And now I want to ask you about another very important day in your lives. Where were you at 4:00 PM on September 8, 1999? That was the day of your "White Coat Ceremony." Dr. Daniel W. Foster, the chairman of the Department of Medicine at Southwestern Medical School in Dallas, was the speaker. Some of his wonderful comments bear repeating (2). First, he reminded you of the four characteristics of the physician as espoused by Sir William Osler. After quoting Osler, Dr. Foster commented, "These, then, are the characteristics of true physicians: to keep the noble heritage, to fight disease, to be constantly progressive, and to remain always benevolent." But then he added, "This life is sometimes hard. You will have hard times in your studies. One is fairly often tired, both as a student and as a practitioner. It is hard also because we do not always win the battle against disease and have to participate in suffering and death." And then Dr. Foster told you a story: "One of my best friends and colleagues on the faculty has a metastatic colon cancer. The outcome is uncertain, but I think it will be easier for him because I will accompany him on that journey. And that will be a privilege. A hard privilege, but a privilege."

I knew that individual. He was also a friend and a colleague of mine. He died last summer. It was, as Dr. Foster noted, a very difficult journey, but made easier because Dr. Foster was there to guide him and his family. You too will have to guide your patients down difficult paths. Never leave, neglect, or abandon them. I remind you of the story because "to teach" has many meanings. You will bring all of them to bear on your patients and on your profession.

In a few moments you will take the Oath of Maimonides and take a vow to live by its principles. This version of the Oath of Maimonides does not speak to teaching others, but stresses constant self-learning — "teach thyself." On White Coat Ceremony Day in September 1999, you took the Oath of Hippocrates. At that time you agreed "to consider dear to me as my parents those who taught me this art, to live in common with them and if necessary to share my goods with them, to look upon their children as my own brothers and sisters, to teach them this art if they so desire without fee or written promise, to impart to my sons and daughters and the children of the Masters who taught me and the disciples who have enrolled themselves and have agreed to the rule of the profession, but to these alone, the precepts and the instruction." Yes, ladies and gentlemen, you took an oath to teach — forsake it not!

And finally, I would ask the graduates one last question. Where were you at noon on March 20, 2003? It was Match Day! On that day you learned where you will begin the next phase of your future careers. And it was a great day for each of you and for the entire class. You exceeded your own expectations as well as the expectations of the school's leadership.

It was Albert Einstein who said, "I never think of the future. It comes soon enough." Your future is here and now. Take it and run with it. Do your job well and the world will beat a path to your door. You will be superb physicians, scientists, counselors and teachers in every sense of the word. You will be respected and admired by your patients, your colleagues and your many students. And if all that happens, as I know it will, you and I will never have to worry about having physicians and scientists for your grandchildren!

One final word. As you go your separate ways, never forget your fellow students and where you began your medical careers. You were fortunate to go to an outstanding medical school that is still in its relative youth, now just 40 years old. You had much of your clinical training in a hospital that has just celebrated its 150th anniversary. When you complete your first 50 years in medicine (which we talked about earlier), this medical school and this hospital will be approaching 100 and 200 years of age, respectively. As of this moment, you become part of a great heritage and a great tradition. You will always be a part of us, and we will always remember you and support you.

All of us in this vast hall wish you the very best, for much luck and success.

Thank you.

References

1. Coller BS. Science and humanism: the twin pillars of medicine. Mt Sinai J Med 2002; 69:277–279.
2. Foster DW. To be a physician. Mt Sinai J Med 2000; 67:133–135.

Cardiovascular Disease in Women

W. Lane Duvall, M.D.

Abstract

Almost 62 million Americans have one or more types of cardiovascular disease and, of these, more than 32 million are female. This translates into an average of 1 in 5 women, making cardiovascular disease the leading killer of women in the U.S., responsible for more than half a million deaths a year.

While it has been known for some time that differences exist between the sexes regarding coronary heart disease, it has only been in the last 10 years that these disparities in incidence, morbidity, mortality, risk factors, diagnosis, and treatment have been explored. Research has shown a gap in the utilization of medical therapy, diagnostic studies, and revascularization procedures involving women. In addition, women's outcomes after myocardial infarction have been consistently demonstrated to be poorer than those of men. Another important issue that has just started to be addressed is that the predominantly male-focused cardiovascular research has been generalized to women. Only in recent years have women been included in clinical trials or databases in sufficient numbers for sex-based analysis of the data.

The topic of cardiovascular disease in women is diverse and complex. In this article, some of the important issues will be introduced and discussed, to highlight our current understanding of the problem and to emphasize the areas in which further study and progress is needed. These issues include the epidemiology of coronary heart disease, the diagnosis of coronary heart disease, the medical therapy of acute coronary syndromes, coronary revascularization, and hormone replacement therapy.

Key Words: Coronary heart disease, women, coronary artery disease, epidemiology, prevention, risk factors, hormone replacement therapy.

Introduction

Of the 61.8 million Americans who have one or more types of cardiovascular disease (CVD), 32.1 million are female (1). This translates into an average of 1 in 5 women. CVD is the number one killer of both men and women in the U.S., resulting in 445,871 deaths among men and 512,904 deaths among women in 1999 (2). Of these deaths, coronary heart disease (CHD) was responsible for 267,268 male deaths and 262,391 female deaths (2). In addition to women accounting for the majority of CVD deaths (53.5%), their mortality from coronary heart disease at presentation is approximately twice that of men (3). Despite the fact that 1 in 2.4 of women's deaths are from CVD and only 1 in 30 are from breast cancer, surveys show that most women are far more afraid of breast cancer than CVD.

While it has been known for some time that differences exist between the sexes regarding CVD, it has only been in the last 10 years that these disparities in incidence, morbidity, mortality, risk factors, diagnosis, and treatment have been explored. During this time there has been a heightened awareness of both sex and gender differences in the delivery of care by the health care community. (Here "sex" refers to biological differences between men and women and "gender" refers to the social and cultural context differences.) The other issue that has just started to be addressed is that the predominantly male-focused cardiovascular research has been generalized to women. Only in recent years have women been included in clinical trials or databases in sufficient numbers for sex-based analysis of the data (4).

The topic of cardiovascular disease in women is complex. This article will attempt to present some of the more important aspects of the topic, to highlight our current understanding as well as to emphasize the areas in which further study and progress is needed.

Fellow in Cardiology, The Zena and Michael Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to W. Lane Duvall, M.D., The Zena and Michael Wiener Cardiovascular Institute, Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; E-mail: william.duvall@mssm.edu

Adapted from a Cardiology Grand Rounds, Controversies in Cardiology presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on April 29, 2002 and updated as of November 2002.

Epidemiology of Coronary Heart Disease in Women

Coronary heart disease remains the leading cause of death among both men and women in the U.S. despite significant advances in the diagnosis and treatment of CHD in the last 30 years. Improvements in therapy for CHD and reduction in the prevalence of CVD risk factors have led to a decline in the CVD death rate in the last three decades. However, this reduction in mortality rates from CVD has not been as pronounced for women as for men, with the recent trend actually toward increasing mortality for women. With the aging of the population, the overall number of CVD deaths has increased recently, and the trend is expected to continue. This trend is especially noticeable among women, who have a longer life expectancy than men.

It is estimated that 12.6 million Americans have CHD, 6.4 million (51%) of them being women, with the lifetime risk of developing CHD after age 40 being 32% for women versus 49% for men (2). The average age of first myocardial infarction (MI) is 70.4 for women and 65.8 for men (2). The prevalence of CVD and CHD in women increases significantly after menopause (2–3 times that of women the same age before menopause) and continues to increase with advancing age. As a rule, the incidence of CHD in women lags behind the incidence in men by approximately 10 years.

Risk Factors

The major traditional risk factors for CHD in women are identical to those for men, and include increasing age, cigarette smoking, hypertension, dyslipidemia, diabetes, family history of premature CHD prior to the age of 65 (55 for men), obesity, and a sedentary lifestyle. Risk factors unique to women include oral contraceptives and menopause. Although the risk factors are similar for both sexes, there are differences in prevalence and magnitude of effect.

Age

The dramatic influence of age on the development of CHD in women was first shown in the Framingham study, which reported a striking 40-fold difference between the oldest age group (75–84 years) and the youngest (35–44 years) (5). The study found a marked sex-associated disparity in the incidence of CHD for the younger age groups, which diminished progressively during middle age, and disappeared almost entirely among the elderly. In women who undergo natural menopause, the clinical onset of CHD and death are, on average, 10 years later than in men, with MI occurring as much as 20 years later. Menopause plays a large role in the effect of aging on CHD; there was a 10-fold increase in CHD risk after menopause, compared to only a 4.6-fold increase in the same age groups in men. The mechanism of the influence of menopause is still unclear, since it may be related to changes in estrogen levels or other age-associated risk factors.

Family History

A family history of premature CHD in a first-degree relative is an important risk factor for both sexes. Because of the later onset of CHD in women, "premature" is defined as before the age of 55 for men and 65 for women. The Framingham study demonstrated an increased relative risk of 1.6 in women with a positive family history, compared to those without one (6). It is believed that family history contributes to CHD risk both through inherited genetic factors and through shared lifestyle characteristics, such as smoking, dietary habits, and physical activity.

Menopause

The incidence of CHD in women increases markedly in middle age, out of proportion to the increase in men, suggesting that menopause, and presumably the loss of ovarian hormones, is deleterious to the heart. The Nurses' Health Study found that women who experienced early surgical menopause without hormonal replacement therapy had 2.2 times the risk of CHD compared to age-matched controls (7).

Cigarette Smoking

Approximately 20% of all deaths from CVD are attributable to smoking, which is the leading preventable risk factor among women. There are estimated to be 22.6 million female smokers — about 21.5% of women in the U.S. (2). The Nurses' Health Study found a clear dose-response relationship between smoking and the risk for CHD (8). In general, studies have shown up to a fourfold increase in risk among heavy smokers and up to a doubling of the risk among light smokers (8, 9). Cigarette smoking triples the risk of MI in premenopausal women and lowers the age of menopause by 1.5–2 years (10). There appears to be a synergistic effect of smoking and oral contraceptive use; there is a significantly increased risk of CHD with both older contraceptives with high-dose estrogen and newer, low-dose contraceptives (11, 12).

Diabetes

Approximately 10.6 million Americans have been diagnosed with diabetes mellitus; of these, 5.7 million (54%) are women and 4.9 million men (2). Diabetes is a more powerful risk factor for women than for men, essentially negating the protective effect of gender even in premenopausal women, so that all diabetic women have a risk of CHD similar to that of diabetic men (13). In the Framingham study, having diabetes increased a woman's risk of a coronary event 5.4-fold versus only 2.4-fold for men (14). Data from the Nurses' Health Study supports these findings, demonstrating a 3- to 7-fold increase in the risk of CVD events in diabetic women (15). Furthermore, women over the age of 45 are twice as likely to develop diabetes compared to men. Diabetes in women is also associated with less favorable outcomes of MI and revascularization. Diabetic women, compared to non-diabetic women, have a substantially worse short- and long-term prognosis after MI than do men, with a higher risk of death, double the risk of reinfarction, and four times the risk of developing heart failure (16–18).

Dyslipidemia

The AMA found that in the U.S. 53.8 million adult women and 48.2 million adult men had total blood cholesterol levels of 200 mg/dL or higher in 1999 (2). Total cholesterol, LDL, and HDL are well-described risk factors for CHD for both men and women (19). Premenopausal women have lower LDL and higher HDL levels than do men. After menopause, however, LDL levels in women rise progressively, so that by old age, women have higher LDL levels than do men. Although HDL levels decline after menopause, they remain higher in women than in men. A large analysis by the National Heart, Lung, and Blood Institute demonstrated that high total and LDL cholesterol levels were a stronger risk factor in young and middle-aged women than in older women, with relative risks of 2.44 (total) and 3.27 (LDL) versus 1.12 and 1.13, respectively (20).

Hypertension

Fifty million people in the U.S. have hypertension (systolic blood pressure greater than 140 mm Hg or diastolic blood pressure higher than 90 mm Hg), representing 1 in 4 adult Americans (2). Up to the age of 55, a higher percentage of men than women have high blood pressure. From 55–74 the ratio shifts towards women. After age 75, the number of women with hypertension is consistently higher than that of men (21). Hypertension is 2–3 times more common in women taking oral contraceptives, especially if they are obese or older (22). The Framingham study reported that hypertensive women are 2.2 times more likely to develop CHD than normotensive women; subsequent studies supported this finding and suggested that the risks were similar for men and women (23).

Physical Inactivity and Obesity

A number of large cohort studies have demonstrated a relationship between physical activity and obesity, and cardiovascular risk and death in women. Epidemiologic study has repeatedly shown that women are more sedentary and more likely to be overweight than are men. Men have a higher prevalence of recommended levels of physical activity, with 33–49% of men and 39–57% of women having no leisure-time physical activity (2). If one uses a body mass index (BMI) of 25 or higher as "overweight" and 30 or higher as "obese," 108.3 million adult Americans can be considered overweight and 44.2 million obese (18.7 million men and 25.6 million women) (2). A recent seven-year follow-up of more than 40,000 postmenopausal women showed a graded, inverse association between physical activity and both all-cause mortality and cardiovascular mortality (24). Follow-up of almost 86,000 women from the Nurses' Health Study evaluated changes in lifestyle in this cohort and attributed a 16% decline in the incidence of CHD to improvement in diet, but an 8% increase in CHD incidence to an increase in BMI (25). Obesity has been demonstrated to be linked to both increased risk of CHD and an increased relative risk of death from CVD of 4.1 compared to the risk level of non-obese women (26–28).

Diagnosis of CHD in Women

While chest pain is the most common presentation of CHD in both sexes, it occurs as the initial presentation of acute MI more frequently in men than in women (29). Atypical and non-chest pain presentations are more common in women, to the extent that it has been suggested that clinical presentation and risk factor analysis are of less value in predicting CHD for women than for men (30). Women are more likely to experience back, jaw, abdominal and neck pain; nausea; shortness of breath; and congestive symptoms. They are less likely to have diaphoresis (29). As a group, women have a higher incidence of silent or unrecognized MI compared to men (31). Women seem to have a greater prevalence of non-cardiac chest pain, and premenopausal women have less angiographically significant coronary artery disease associated with their chest pain than do men. However, at the same time, women are more likely to present with angina than MI as the initial symptom of CHD. Women are also more likely to attribute their symptoms to non-cardiac etiologies, due to their relatively low awareness of their risk of CHD. The diagnosis of CHD in women is more challenging and problematic due to these atypical characteristics of their symptoms, but also due to less certainly in interpreting the results of diagnostic testing.

Exercise Stress Testing

Exercise electrocardiography (ECG) is the most readily available and least costly tool for the diagnosis of CHD, but has been found to be less accurate for women than for men. A meta-analysis of ECG testing of women found a sensitivity of 61% and a specificity of 70% (32) compared to a meta-analysis involving men, which demonstrated a sensitivity of 68% and a specificity of 77% (33). There have been many explanations proposed for this discrepancy in accuracy, including lower prevalence of disease in women, less extensive disease in women, lower heart rate responses to exercise, more frequent repolarization abnormalities on baseline ECGs, and the effect of estrogen on the ST segment (34). Despite the lower accuracy for women, diagnostic scores applied to exercise testing have been tested and validated for them. The Duke Treadmill Score is a weighted index combining ST segment deviation, treadmill time and angina, which provides accurate diagnostic and prognostic information for women with suspected CHD (35).

The optimal strategy for diagnosing CHD in women is controversial and the role of exercise ECG uncertain, but any strategy should take into account the pre-test probability of disease in women (36). For women with a low probability of CHD (less than 20%), exercise ECG is usually not recommended because of the possibility of false-positive results and the resultant unnecessary follow-up testing. This population includes young, premenopausal women without risk factors who are at very low risk for CHD. But if an exercise ECG is performed, a negative test has a high negative predictive value and should be trusted, and imaging procedures would not be needed. For women with a high likelihood of CHD (greater than 80%), the most effective strategy may be to proceed directly to catheterization. For the intermediate risk group, there are controversial opinions on how to proceed, because of the sex-specific deficiencies of exercise ECG. The American College of Cardiology/American Heart Association (ACC/AHA) recommends that some form of imaging should be added to the study when there are baseline ECG abnormalities, but as a whole, the negative predictive value for this subset of women is good, with the likelihood of a false negative test actually being lower for women than for men (37).

Nuclear Stress Testing

The use of nuclear tracers such as thallium or technetium for myocardial perfusion imaging adds additional information beyond that of exercise ECG testing alone, because it can identify the presence of coronary artery disease (CAD) and determine its severity. A meta-analysis of thallium imaging for women demonstrated a sensitivity of 78% and a specificity of 64% (32). Results for women may also be less accurate than those for men with this diagnostic modality due to attenuation artifacts and artifacts caused by smaller left ventricular chamber sizes. Soft tissue attenuation from breast tissue most commonly causes defects in the anterior and septal distributions, which may erroneously be reported as infarction or even ischemia if breast tissue shifts during the study. Smaller ventricular chamber size, which is more common in women due to their smaller body surface area (BSA), causes a blurring artifact, reducing the accuracy of the study. The higher energy radioisotope technetium decreases the problem of breast attenuation and allows for easier gated image acquisition. The improvement in soft tissue attenuation technology made possible by technetium has helped normalize the accuracy between men and women without an overall decline in sensitivity. In a study comparing thallium with technetium in women, investigators found a similar sensitivity but a higher specificity (82%, improved to 92% with ECG gating for technetium compared to 67% for thallium) (38).

Most important, myocardial perfusion imaging is an independent predictor of cardiac events or death. In many studies, after adjustment for other exercise variables, the number of abnormal territories has been the most consistent predictor of mortality. Most studies have shown that increased event rates, based on abnormal imaging and low yearly event rates with normal imaging, are similar for men and women (39, 40).

Stress Echocardiography

Echocardiography can be used in conjunction with exercise testing or pharmacologic stress for the diagnosis of CHD. A meta-analysis of both sexes of exercise stress echocardiography revealed a sensitivity of 85% and specificity of 77% (41), while a second meta-analysis of women showed a sensitivity and specificity of 86% for pharmacologic stress echocardiography (42). A normal stress echocardiogram, either exercise or pharmacologic, portends an excellent prognosis, with cardiac event rates of 1–4% over 3 or more years of follow-up. In other studies, positive echocardiographic result added incremental prognostic value to that provided by the ECG portion of the test, with event rates up to four times higher than for women with negative tests (43–46). Based on reported data, neither nuclear perfusion imaging nor stress echocardiography has proven to be superior; rather, they provide comparable results for the diagnosis of CAD (47). While stress echocardiography may have a slightly higher specificity and be less costly, 5–10% of studies may have poor or incomplete imaging due to technically difficult views. Nuclear imaging, on the other hand, provided extensive data on the prognosis of positive and negative studies, but suffers from the problem of breast attenuation (34).

Medical Therapy of Acute Coronary Syndromes in Women

Nowhere is the discrepancy between the sexes greater than in the morbidity and mortality resulting from myocardial infarction. MIs are lethal more often for women than for men, regardless of age or comorbidity (48), and both 30-day and one-year crude mortality rates for women after having an MI are nearly double those for men (49, 50). In the 26-year follow-up of the Framingham study, the overall case fatality rate was 32% for women and 27% for men (5). Based on data from the AHA, 25% of men and 38% of women will die within 1 year of having an initial recognized MI (2). Within 6 years of a recognized MI, 18% of men and 35% of women will have another MI, and 22% of men and 46% of women will be disabled with heart failure (2). Even when confounding variables are taken into account, women who have a clear indication for thrombolytic therapy in recent trials have an approximately 15% higher mortality rate than men (49, 50). However, a more recent analysis of a U.S. Medicare population did not show any differences between the sexes in early mortality after MI (51).

Several factors contribute to a worse outcome for women. Upon presentation, women are older, have more comorbidities including diabetes and hypertension, and have more complications such as reinfarction, pulmonary edema, shock, and cardiac rupture (52). Other factors may also play a role, such as delayed presentation to the emergency room, reduced perception of risk of MI by women and health care providers, and atypical, more transient symptoms at presentation (53, 54). Women are also more likely to present with non-ST segment elevation MIs and unstable angina than with ST-elevation MIs. This makes diagnosis more difficult to establish and longer to accomplish (55). Even with all these factors, women with the same symptoms as men are less likely to be admitted to the coronary care unit than are men. These sex-specific differences in MIs are not clearly understood and are sometimes counterintuitive. For example, women have more complications than do men despite having less significant CAD, and women have more CHF than men despite having better left ventricular function (54).

From the data accumulated from clinical trials, it appears that there is no significant difference between men and women with regard to the beneficial effects of the various medical therapies for acute coronary syndromes. Large clinical studies looking at the improvement in morbidity and mortality for those taking aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, thrombolytics and others have shown no significant difference between the sexes. However, these therapies may be received less often by women than by men (56). And the data gathered from these clinical trials may actually underestimate morbidity and mortality for women, since all eligible participants receive the planned treatment regardless of age or sex. While women have equivalent infarct artery patency rates after thrombolytics, they are less likely to receive thrombolytics, with only 55% of women, compared to 78% of men, receiving them when indicated, according to the Myocardial Infarction Triage and Intervention Registry (MITI) (57). The discrepancy of women being less likely to receive standard medical therapy also applies to aspirin, beta-blockers, and heparin, with aspirin being used by only 55% of women compared to 70% of men (58). ACE inhibitors seem to be the one exception to this trend, possibly due to a higher incidence of heart failure in women with MI. In general, only 18–25% of subjects in the thrombolytic trials have been women. This is similar to the observed enrollment of approximately 20% in studies of glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparin, which limits the ability to develop sex-specific conclusions.

Coronary Revascularization in Women

Because many of the large trials of CHD treatment have not included women or have included them in very small numbers, the applicability of these studies to women with regard to revascularization strategies remains somewhat speculative. In addition, fewer women than men are referred for invasive testing or interventional strategies, further compromising the ability to evaluate strategies in women.

It was first reported in 1987 that there was a gender bias in referral for cardiac catheterization and, therefore, for considering coronary artery bypass graft (CABG) (59). This lower referral rate for coronary angiography for women has been substantiated in subsequent trials such as Survival and Ventricular Enlargement (SAVE) and TIMI III (60, 61). A report from the National Registry of Myocardial Infarction in 1998 stated that, despite having a higher mortality rate after MI than men, women had lower rates of cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), and CABG (62). Reasons for these lower rates of coronary angiography for women remain unclear. Difficulties in diagnosis due to atypical presentation in women, poor sensitivity and specificity of diagnostic testing, or even simply poor access to resources may all contribute. Furthermore, the advanced age of women with CHD, misperceptions that CHD rarely affects women or that when women have CHD it is very advanced and they are unlikely to benefit from interventions, may also play a role.

Percutaneous Intervention

All early studies and virtually all registry data on percutaneous interventions have suggested that women do not fare as well as men following coronary angioplasty. Registries, which may provide the best insight into "real life" practices, as opposed to highly structured clinical trials, have consistently shown significantly higher mortality and complication rates for women than for men. In all of these studies, the women were older than the men and had more comorbidities and less body surface area. The higher mortality and complication rates have been blamed on these differences of age, comorbidities, smaller vessel size due to smaller body surface area, and potentially later presentation. A large collection of data from the National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry from 1985–1986 revealed female sex to be an independent risk factor for death (Risk Ratio [RR] 4.53) (63). Women in this registry were older and had more risk factors, more severe angina, higher initial complications and higher mortality rates than did men, but they did not have more extensive CAD than men. Other registries from Emory University for 1982–1986 (64), from the Mayo Clinic for 1979–1990 (65), and from the Cleveland Clinic for 1980–1985 (66), supported these findings and confirmed female sex to be a risk factor for death, but the latter two studies concluded that the increased mortality rate was related to body surface area and that sex itself was not an independent risk factor.

Randomized trials of coronary interventions have historically included a very small percentage of women, with an average inclusion rate of 20–30% (67). In any event, randomized trials have generally failed to support early registry findings and have not shown any significant difference between men and women with regard to referral or revascularization outcomes. The GUARANTEE study evaluated nearly 3,000 consecutive patients (39% women) admitted for unstable angina in 1996, and did show that cardiac catheterization, PTCA, and CABG were performed less often on women (56). However, after controlling for relative clinical severity of men and women, the study found that both sexes were appropriately referred to angioplasty at a similar rate. Despite this, fewer women underwent CABG than men. There was, however, no difference between the sexes in the rate of recurrent angina, in-hospital infarction, and death among those undergoing all interventional procedures. The BARI study evaluated more than 1,800 patients (27% women) randomized to PTCA or CABG and found that the women included were older, with more comorbidities, but had similar mortality rates after 5.4 years of follow-up (68). And contrary to previous reports, the investigators actually found that female sex was an independent predictor of improved five-year survival.

Coronary Artery Bypass Graft

Most series of bypass surgery have had a large preponderance of male patients, and as with percutaneous interventions, female sex itself was felt to be an independent risk factor for surgery (69). It is this conception that may have led in part to the bias against referral of women for cardiac catheterization and CABG (70). It is clear, however, that women presenting for bypass surgery have different clinical characteristics than men. Women are consistently older and have more comorbid conditions such as diabetes, hypertension, and peripheral vascular disease; they present with more severe angina and often require surgery on a more urgent basis (71). On the other hand, women tend to have less extensive CAD than do men and have better preservation of left ventricular function (71).

The significance of sex as an independent risk factor for CABG is debatable, and in all likelihood it is the differences in risk factors that contribute most to operative mortality and long-term survival. Explanations for the observation that female sex has been reported to result in higher mortality after CABG include the smaller size of women's coronary arteries, which presents a technical challenge; a referral bias that causes women to present at a more advanced stage of the disease; and an increased number of comorbidities in women (67). The largest registry of CABG results, the Society of Thoracic Surgery database, contains information on more than 300,000 patients (28% women) (72). An analysis of this database found that sex was an independent risk factor related to operative mortality and that risk factors were almost identical for both sexes, although the relative weight was different depending on the sex. Body size was also clearly related to mortality, with increased mortality with decreasing size. Most reported series demonstrate that women receive fewer arterial grafts than do men; most important, they receive fewer left internal mammary arteries to the left anterior descending artery. While some studies have shown an increased incidence of angina or recurrent MI over time in women after CABG (73), recent studies have shown similar improvement in functional status after surgery (74) and comparable long-term survival in men and women (75).

Hormone Replacement Therapy

Use of hormone replacement therapy (HRT) for menopausal symptoms, osteoporosis, and CHD has been controversial, due to the increased risk of breast and endometrial cancer as well as venous thromboembolism, and possible lack of efficacy resulting from its use. Because of the observed twofold increase in risk of CHD following natural menopause or premature ovarian failure, the beneficial effects of estrogen on the lipid profile, and estrogen's effect on vascular reactivity and endothelial function, ovarian estrogen is felt to be cardioprotective. The argument in favor of estrogen is further bolstered by the observations that men between the ages of 30 and 50 are at higher risk for CVD than are premenopausal, non-diabetic women, and the rate of increase in atherosclerotic lesions in women aged 50–70 is higher than for men. Multiple earlier observational studies have suggested that HRT is associated with a 40–50% reduction in CHD risk, but recent prospective studies have cast doubt on this, suggesting that the findings might instead be related to healthier risk factor profiles for women on HRT (76).

Effects on Lipid Profile

After menopause, as a result of estrogen withdrawal and weight gain, there is a decrease in HDL and an increase in LDL. Oral estrogen replacement therapy increases HDL and decreases LDL. After oral administration, high concentrations of estrogen reach the liver via the portal circulation. This results in increased expression of the LDL receptor and apolipoprotein AI and decreased expression of hepatic lipase, leading to a reduction in LDL and an increase in HDL. Estrogen also increases hepatic triglyceride synthesis and can cause hypertriglyceridemia. Transdermal estrogen does not have the same adverse effects on triglycerides, but it also does not increase HDL concentrations (77).

Randomized clinical trials have evaluated the effects of HRT on lipid profiles. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial looked at estrogen alone and estrogen plus either medroxyprogesterone or micronized progesterone (78). All treatments decreased LDL by 14.5–17.7 mg/dL (12–14%) and increased triglycerides by 11.4–13.7 mg/dL (15%). However, the effect on HDL varied: the biggest increase in HDL was 5.6 mg/dL (11%), in the estrogen only group; the smallest increase was 1.2–1.6 mg/dL (3%), in the medroxyprogesterone group. Unopposed estrogen, however, was associated with an increased risk of endometrial hyperplasia and should therefore be limited to women without a uterus. Raloxifene is a selective estrogen modulator — a non-hormonal agent that binds to the estrogen receptor and exhibits agonist or antagonist effects, depending on the target tissue — that has been developed with the hope of lessening some of the side effects of HRT. In a randomized trial, raloxifene decreased LDL by 12%, the same as standard HRT, and had no effect on triglyceride levels, but did not increase HDL levels (79).

Vascular Reactivity and Endothelial Function

There is mounting evidence that estrogen improves vascular reactivity and endothelial function. Vascular reactivity, a blood vessel's ability to dilate in response to a stimulus, is measured as sublingual nitroglycerin-induced brachial artery flow and is felt to facilitate reperfusion to ischemic tissue. Studies have shown that this response to nitroglycerin is lower in men than in women, and that vascular reactivity becomes impaired in postmenopausal women but recovers when they are given HRT (80). The endothelium plays an important role in atherosclerotic disease, since it serves to produce important vasodilating factors, thereby regulating vascular tone; inhibits platelet adhesion; and maintains a balance between thrombosis and fibrinolysis. Early studies have shown that HRT improves endothelial function by increasing nitric oxide production and by mitigating age-related changes in arterial structure and function (81, 82).

Primary and Secondary Prevention

Because of all the beneficial effects of estrogen on surrogate endpoints and the observed sharp rise in CHD after menopause, HRT appeared to be a straightforward intervention for primary and secondary prevention of CHD and MI in postmenopausal women. Multiple observational studies in the past 10–15 years have supported this conclusion by demonstrating lower rates of CHD events in postmenopausal women who use HRT. Meta-analyses of these epidemiologic findings concluded that HRT reduced the risk of CHD by 35–50% (83, 84). The risk reduction for secondary prevention based on study data appeared to be even higher, at 35–80% (85–88). These observational studies all show lower risks of CHD, reinfarction, cardiac death, and restenosis. However, there have always been reasons to view these observational results of HRT in women cautiously. Consistently, women who took HRT were better educated, had fewer risk factors for CHD, were less likely to be obese or to smoke, and were more likely to follow a low-fat diet and be physically active. Although statistical approaches are used to compensate for such differences, it remains difficult to control for all confounders and impossible to control for unknown confounders. This bias towards a protective effect in users of HRT has been called "prevention bias" (89). "Compliance bias," which represents another potential bias affecting observational trials of HRT, refers to the reduction in relative risk of CHD found for subjects who were compliant in taking their medications versus those who were not. In fact, it is estimated that only 25–40% of women continue to take postmenopausal hormone therapy for more than one year. This bias has been measured in studies comparing subjects who faithfully took placebo versus those who did not, and in subjects who did and did not regularly take the active drug, and was found to represent a relative risk reduction of 30% (90).

The largest cohort for observational data o HRT in CHD comes from the more tha 121,000 women enrolled in the Nurses' Healt Study, which started in 1976. The nurse-subjects were between the ages of 30 and 55 at enrollment, and data were collected by biennia questionnaires. There were 3,637 deaths ove 18 years, and after correction for confoundin variables, hormone users had a lower risk of death than those who had never used hormones (RR 0.63) (91). However, this benefit decreased with time, to a relative risk of 0.80 after 10 years, which was attributed to the increasing risk of breast cancer. The greatest reduction in risk of death among women taking HRT was found in the group with high CHD risk factors (RR 0.51), and the least reduction was found in those at low risk for CHD (RR 0.89). The Nurses' Health Study had published three earlier analyses of data at different timepoints, also showing an approximately 40% risk reduction of CHD in women taking HRT (92–94). Subsequent publications have tried to determine the effect of HRT on primary and secondary prevention. In the more than 70,000 subjects without CHD, 1,258 major coronary events occurred over 20 years. After taking into account known confounders, the risk for major coronary events was lower among current HRT users, including short-term users, compared with never-users (RR 0.61) (95). In looking at 2,489 women with known CHD, 213 recurrent events or cardiac death were found again, with a lower risk of recurrent events among HRT users (RR 0.65) (96). However, short-term users (< 1 year) had a higher relative risk of events (1.25) compared with never-users, while the relative risk of a second event for long-term users (> 2 years) was only 0.38.

In 1998, when the Heart Estrogen/progestin Replacement Study (HERS) was published, the data from observational studies seemed overwhelming, to the point where it was felt that it was almost unethical to randomize women to placebo in future trials. The HERS trial randomized 2,763 postmenopausal women with CHD and an intact uterus to estrogen and progesterone or placebo and followed them for an average of 4.1 years (97). A majority of subjects had significant CHD and important risk factors, with 42% having had CABG, 45% having had percutaneous coronary intervention (PCI), 62% being current or past smokers, 59% with hypertension, and 23% being diabetic. Despite an improvement in lipid profile, with an 11% decrease in LDL and a 10% increase in HDL, there was no significant difference in death due to MI or CHD between the two groups (Relative Hazard [RH] 0.99). However, there was a significant time trend from the time of randomization. There were more CHD events in the HRT group during the first year than in the placebo group (RH 1.57), but during the last two years this trend reversed, with fewer events in the HRT group (RH 0.67). Explanations for the time trend of HRT include an early prothrombotic effect of HRT, with the later benefit representing the true effect of HRT. Alternatively, it is possible that all of the high-risk patients died early, leaving a low-risk cohort behind. HERS II consisted of an additional 2.7 years of unblinded follow-up of 2,321 (93%) of the original HERS subjects, in an attempt to explain this time trend (98). HERS II showed that the lower rates of CHD events among women in the HRT group in the final years of HERS did not persist during the additional years of follow-up, with an RH of 1.00 during HERS II and an RH of 0.99 during the entire 6.8 years of HERS and HERS II. In addition, HRT during the 6.8 years of total follow-up significantly increased the risk of venous thromboembolism (RH 2.08) and biliary tract surgery (RH 1.48) (99). As a result of these studies, the AHA recommends that HRT should not be initiated for secondary prevention of CVD and that physicians should consider discontinuation of HRT if a women develops CHD (100).

The Women's Health Initiative (WHI) enrolled more than 27,000 patients between 1993 and 1998, and is expected to conclude in 2005. These subjects, between the ages of 50 and 79, were for the most part without a history of heart disease; 60% of them were randomized to HRT or placebo, while the other 40%, who had undergone a hysterectomy, were randomized to estrogen-only or placebo. In May 2002, the Data and Safety Monitoring Board discontinued the combination HRT arm of the study, involving 16,608 subjects with an average follow-up of 5.2 years, citing an increased risk of invasive breast cancer in those taking HRT versus placebo (101). At the interim analysis, the test statistic for invasive breast cancer exceeded the stopping boundary, and the overall risks of therapy outweighed the benefits. In particular, there was a statistically significant increased risk of CHD (HR 1.29), stroke (HR 1.41), breast cancer (HR 1.26), and thromboembolic events (HR 2.11). The benefits of HRT included statistically significant reductions in colorectal cancer (HR 0.63) and fractures (HR 0.76). Overall, there was no significant difference in all-cause mortality. Based on this data, the study investigators concluded that the risks of HRT outweigh the benefits and that HRT should not be initiated or continued for the primary prevention of CHD.

Two other important randomized trials of HRT have been published. The estrogen replacement study randomly assigned 309 women with angiographically proven coronary disease to estrogen, estrogen plus progesterone, or placebo; the subjects received a repeat angiogram, on average, some 3.2 years later (102). Neither estrogen nor estrogen plus progesterone affected the progression of coronary disease in this population. A secondary analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a randomized and blinded study of nearly 8,000 postmenopausal women, on the effects of raloxifene on bone mineral density, was undertaken to determine the cardiovascular effects of the drug (103). In the overall cohort, after four years there was no significant difference between the treatment groups and placebo with regard to the number of CHD events. However, among the subset of 1,035 women at increased CVD risk, there was a significant risk reduction in cardiovascular events (RR 0.60). Further analysis of events during the first year of therapy did not indicate any increased risk in either the overall cohort or in those at increased CVD risk.

The data from HERS, HERS II, and the WHI did not address all of the issues surrounding HRT and CHD, including the use of unopposed estrogen, alternative HRT regimens, and especially HRT's role in primary prevention. Several randomized studies are currently underway which may shed further light on the HRT issue. The WHI is still following more than 11,000 patients who had undergone a hysterectomy, who were randomized to estrogen-only or placebo; results are expected in 2005. Another similar study, the Women's International Study of Long-Duration Oestrogen after Menopause (WISDOM), is currently recruiting 34,000 women without pre-existing heart disease. In secondary prevention, the Estrogen in the Prevention of Reinfarction Trial (ESPRIT) is currently ongoing. There are also three ongoing angiographic studies of HRT in women with pre-existing heart disease. These studies, which are expected to yield results in the near future, are the Women's Lipid Lowering Heart Atherosclerosis (WELL-HEART), the Women's Angiographic Vitamins and Estrogen (WAVE), and the Estrogen and Graft Atherosclerosis (EAGAR) trials.

Conclusions

Cardiovascular disease is the leading killer of women in the U.S., responsible for more than half a million deaths a year. CVD in women is a diverse and complex topic that in recent years has been dominated by the issue of HRT and the controversy started by the HERS study. While HRT brings to light issues of procoagulation, thrombosis, and inflammation, it should not overshadow the discrepancies in care, outcome, and research between the sexes. Research has shown a gap in the utilization of medical therapy, diagnostic studies, and revascularization procedures involving women. This gap has not been adequately addressed. Women's outcomes after MI have been consistently demonstrated to be well below those of men. And finally, only about 20% of subjects enrolled in cardiovascular research have been women, severely limiting our ability to resolve these and other important issues.

References

1. National Health and Nutrition Examination Survey III (NHANES III), 1988-94, CDC/NCHS and the American Heart Association.
2. American Heart Association. 2002 Heart and stroke statistical update. Dallas, Texas: American Heart Association, 2001
3. Brister SJ, Turek MA. Introduction to women and ischemic heart disease. Can J Cardiol 2001; 17(Suppl D):5D–6D.
4. Harris DJ, Douglas PS. Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. N Engl J Med 2000; 343:475–480.
5. Lerner DJ, Kannel WB. Patterns of coronary heart disease mortality and morbidity in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986; 111:383–390.
6. Schildkraut JM, Meyers RH, Cupples LA, et al. Coronary risk associated with age and sex of parental heart disease in the Framingham Study. Am J Cardiol 1989; 64:555–559.
7. Colditz GA, Willett WC, Stampfer MJ, et al. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987; 316:1105–1110.
8. Willett WC, Green A, Stampfer MJ, et al. Relative and absolute risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1987; 317:1303–1309.
9. Bartecchi C, Mackenzie T, Schrier R. The human costs of tobacco use. N Engl J Med 1994; 330:907–912.
10. Hansen EF, Andresen LT, von Eyben FE. Cigarette smoking and age at first myocardial infarction and influence of gender and extent of smoking. Am J Cardiol 1993; 171:1439–1442.
11. Stradel B. Oral contraceptives and cardiovascular disease. N Engl J Med 1981; 305:672–677.
12. Thorgood M, Mann J, Murphy M, Vessey M. Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case control study. Br J Obstet Gynecol 1991; 98:1245–1253.
13. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA 1991; 265:627–631.
14. Kannel WB, McGee DL. Diabetes and glucose intolerance as risk factors for cardiovascular disease: the Framingham Study. Diabetes Care 1979; 2:120–126.
15. Manson JE, Rimm EB, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 1991 151:1141–1147.

16. Abbott RD, Donahue RP, Kannel WB, Wilson P. The impact of diabetes on survival following myocardial infarction in men vs women: the Framingham Study. JAMA 1988; 260; 3456–3460.
17. Savage MP, Krolewski AS, Kenien GG, et al. Acute myocardial infarction in diabetes mellitus and significance of congestive heart failure as a prognostic factor. Am J Cardiol 1988; 62:665–669.
18. Chun BY, Dobson AJ, Heller RF. The impact of diabetes on survival among people with first myocardial infarction. Diabetes Care 1997; 20:704–708.
19. Castelli WP, Garrison RJ, Wilson P, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. JAMA 1986; 256:2835–2838.
20. Manolio TA, Pearson TA, Wenger NK, et al. Cholesterol and heart disease in older persons and women: review of an NHLBI workshop. Ann Epidemiol 1992; 2:161–176.
21. Cornoni-Huntley J, LaCroix AZ, Havlik RJ. Race and sex differentials in the impact of hypertension in the United States: the National Health and Nutrition Examination Survey: I — Epidemiologic follow-up study. Arch Intern Med 1989; 149:780–788.
22. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Int Med 1997; 157:2413–2446.
23. Stokes J, Kannel WB, Wolf PA, et al. Blood pressure as a risk factor for cardiovascular disease: the Framingham Study — 30 years of follow-up. Hypertension 1989; 13(Suppl I):I13–I18.
24. Kushi LH, Fee RH, Folsom AR, et al. Physical activity and mortality in post-menopausal women. JAMA 1997; 277:1287–1292.
25. Hu FB, Stampfer MJ, Manson JE, et al. Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. N Engl J Med 2000; 343:530–537.
26. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67:968–977.
27. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 1990; 322:882–889.
28. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. N Engl J Med 1995; 333:677–685.
29. Zucker DR, Griffith JL, Beshansky JR, Selker HP. Presentation of acute myocardial infarction in men and women. J Gen Intern Med 1997; 12:79–87.
30. Sullivan AK, Holdright DR, Wright CA, et al. Chest pain in women: clinical, investigative, and prognostic features. BMJ 1994; 308:883–886.
31. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction: an update on the Framingham study. N Eng J Med 1984; 311:1144–1147.
32. Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999; 83:660–666.
33. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation 1989; 80:87–98.
34. Isaac D, Walling A. Clinical evaluation of women with ischemic heart disease: diagnosis and noninvasive testing. Can J Cardiol 2001; 17 Suppl D:38D–48D.
35. Alexander KP, Shaw LJ, Shaw LK, et al. Value of exercise treadmill testing in women. J Am Coll Cardiol 1998; 32:1657–1664.
36. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Eng J Med 1996; 334:1311–1315.
37. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997; 30:260–311.
38. Taillefer R, DePuey EG, Udelson JE, et al. Comparative diagnostic accuracy of TI-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. J Am Coll Cardiol 1997; 29:69–77.
39. Marwick TH, Shaw LJ, Lauer MS, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Economics of Noninvasive Diagnosis (END) Study Group. Am J Med 1999; 106(2):172–178.
40. Travin MI, Duca MD, Kline GM, et al. Relation of gender to physician use of test results and to the prognostic value of stress technetium 99m sestamibi myocardial single-photon emission computed tomography scintigraphy. Am Heart J 1997; 134:73–82.
41. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA 1998; 280:913–920.
42. Tong AT, Douglas PS. Stress echocardiography in women. Cardiol Clin 1999; 17:573–582.
43. McCully RB, Roger VL, Mahoney DW, et al. Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: follow-up of 1,325 patients. J Am Coll Cardiol 1998; 31:144–149.
44. Heupler S, Mehta R, Lobo A, et al. Prognostic implications of exercise echocardiography in women with known or suspected coronary artery disease. J Am Coll Cardiol 1997; 30:414–420.
45. Cortigiani L, Dodi C, Paolini EA, et al. Prognostic value of pharmacological stress echocardiography in women with chest pain and unknown coronary artery disease. J Am Coll Cardiol 1998; 32:1975–1981.
46. Chuah SC, Pellikka PA, Roger VL, et al. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. Circulation 1998; 97:1474–1480.
47. O'Keefe JH, Barnhart CS, Bateman TM. Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity. Am J Cardiol 1995; 75:25D–34D.
48. Marrugat J, Sala J, Masia R, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. JAMA 1998; 280:1405–1409.
49. Weaver WD, White HD, Wilcox RG, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. Gusto-I Investigators. JAMA 1996; 275:777–782.
50. Malacrida R, Genoni M, Maggioni AP, et al. A comparison of the early outcome of acute myocardial infarction in women and men. The Third International Study of Infarct Survival Collaborative Group. N Eng J Med 1998; 338:8–14.
51. Gan SC, Beaver SK, Houck PM, et al. Treatment of acute myocardial infarction and 30-day mortality among women and men. N Eng J Med 2000; 343:8–15.
52. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. Circulation 1991; 83:484–491.

53. Clarke KW, Gray D, Keating NA, Hampton JR. Do women with acute myocardial infarction receive the same treatment as men? BMJ 1994; 309:563–566.
54. Kudenchuk PJ, Maynard C, Martin JS, et al. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (The Myocardial Infarction Triage and Intervention Registry). Am J Cardiol 1996; 78:9–14.
55. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Eng J Med 1999; 341:226–232.
56. Scirica BM, Moliterno DJ, Every NR, et al. Differences between men and women in the management of unstable angina pectoris (The GUARANTEE Registry). Am J Cardiol 1999; 84:1145–1150.
57. Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction. Results from the Myocardial Infarction Triage and Intervention Registry. Arch Intern Med 1992; 152(5): 972–976.
58. Schwartz LM, Fisher ES, Tosteson NA, et al. Treatment and health outcomes of women and men in a cohort with coronary artery disease. Arch Intern Med 1997; 157:1545–1551.
59. Tobin JN, Wassertheil-Smoller S, Wexler JP, et al. Sex bias in considering coronary bypass surgery. Ann Intern Med 1987; 107:19–25.
60. Steingart R, Packer M, Hamm P, et al. Sex differences in the management of coronary artery disease: Survival and Ventricular Enlargement investigators. N Eng J Med 1991; 325:226–230.
61. Stone PH, Thompson B, Anderson H, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction in the United States and Canada (the TIMI III Registry). JAMA 1996; 275:1104–1112.
62. Chandra NC, Ziegelstein RC, Rogers WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med 1998; 158:981–988.
63. Kelsey S, James M, Holubkov AL, et al. Results of percutaneous transluminal coronary angioplasty in women. 1985–1986 National Heart, Lung, and Blood Institute Coronary Angioplasty Registry. Circulation 1993; 87:720–727.
64. Ellis SG, Myler RK, King SB, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation 1988; 77:372–379.
65. Bell MR, Holmes DR, Berger PB, et al. The changing in-hospital mortality of women undergoing percutaneous transluminal angioplasty. JAMA 1993; 269:2091–2095.
66. Arnold AM, Mick MJ, Piedmonte MR, Simpfendorfer C. Gender differences for coronary angioplasty. Am J Cardiol 1994; 74:18–21.
67. Kells CM, Mickleborough L. Revascularization strategies in women with ischemic heart disease. Can J Cardiol 2001; 17(Suppl D):53D–56D.
68. Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). Circulation 1998; 98:1279–1285.
69. Hall RJ, Elayda MA, Gray A, et al. Coronary artery bypass: long-term follow-up of 22,284 consecutive patients. Circulation 1983; 68(Suppl II):II20–II26.
70. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. N Eng J Med 1991; 325:221–225.
71. Mickleborough LL, Takagi Y, Maruyama H, et al. Is sex a factor in determining operative risk for aortocoronary bypass graft surgery? Circulation 1995; 92(Suppl II):II80–II84.
72. Edwards FH, Grover FL, Shroyer AL, et al. The Society of Thoracic Surgeons National Cardiac Surgery Database: current risk assessment. Ann Thorac Surg 1997; 63:903–908.
73. Brandrup-Wognsen G, Berggren H, Hartford M, et al. Female sex is associated with increased mortality and morbidity early, but not late, after coronary artery bypass grafting. Eur Heart J 1996; 17:1426–1431.
74. Stewart RD, Blair JL, Emond CE, et al. Gender and functional outcome after coronary artery bypass. Surgery 1999; 126:184–190.
75. Davis KD, Chaitman B, Ryan T, et al. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS registry study. J Am Coll Cardiol 1995; 25:1000–1009.
76. Sites CK. Hormone replacement therapy: cardiovascular benefits for aging women. Coron Artery Dis 1998; 9:789–793.
77. Walsh BW, Schiff I, Rosner B, et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med 1991; 325:1196–1204.
78. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. JAMA 1995 Jan 18;273(3):199–208.
79. Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA 1998; 279:1445–1451.
80. Perregaux D, Chaudhuri A, Mohanty P, et al. Effect of gender differences and estrogen replacement therapy on vascular reactivity. Metabolism 1999; 48:227–232.
81. Best PJ, Berger PB, Miller VM, Lerman A. The effect of estrogen replacement therapy on plasma nitric oxide and endothelin-1 levels in postmenopausal women. Ann Intern Med 1998; 128:285–288.
82. McGrath BP, Liang YL, Teede H, et al. Age-related deterioration in arterial structure and function in postmenopausal women: impact of hormone replacement therapy. Arterioscler Thromb Vasc Biol 1998; 18:1149–1156.
83. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991; 20:47–63.
84. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Int Med 1992; 117:1016–1037.
85. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. Arch Intern Med 1991; 151:75–78.
86. O'Brien JE, Peterson ED, Keeler GP, et al. Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions. J Am Coll Cardiol 1996; 28:1111–1118.
87. Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. Am J Cardiol 1997; 79:847–850.
88. O'Keefe JH, Kim SC, Hall RR, et al. Estrogen replacement therapy after coronary angioplasty in women. J Am Col Cardiol 1997; 29:1–5.
89. Barrett-Connor E. Postmenopausal estrogen and prevention bias. Ann Intern Med 1991; 115:455–456.
90. Petitti DB. Coronary heart disease and estrogen replacemen therapy: can compliance bias explain the results of observa tional studies? Ann Epidemiol 1994; 4:115–118.

91. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. N Engl J Med 1997; 336:1769–1775.
92. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. N Eng J Med 1985; 313:1044–1049.
93. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the Nurses' Health Study. N Eng J Med 1991; 325:756–762.
94. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Eng J Med 1996; 335:453–461.
95. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000; 133:933–941.
96. Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study. Ann Intern Med 2001; 135:1–8.
97. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in women. JAMA 1998; 280:605–613.
98. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and estrogen/progestin replacement study follow-up (HERS II). JAMA 2002; 288:49–57.
99. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and estrogen/progestin replacement study follow-up (HERS II). JAMA 2002; 288:58–66.
100. Mosca L, Collins P, Herrington D, et al. Hormone replacement therapy and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. Circulation 2001; 104:499–503.
101. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321–333.
102. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Eng J Med 2000; 343:522–529.
103. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women. Four year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 2002; 287:847–857.

The Electrocardiogram as a Predictor of Left Ventricular Systolic Function:

Correlation with Gated SPECT Imaging

Milena J. Henzlova, M.D.[1], and Lori B. Croft, M.D.[2]

Abstract

Background: Left ventricular systolic function, expressed as ejection fraction (LVEF), is an important determinant of prognosis for cardiac disease, and is the basis for therapeutic decisions. Several imaging modalities are used for measuring LVEF. All require time, appropriate technology and professional attention, and most expose patients to small doses of radiation. We studied the correlation between surface electrocardiogram (ECG) and nuclear angiography in 673 patients. The purpose of our study was to determine whether normal ECG reliably predicts normal LVEF. Gated single-photon emission computed tomography (GSPECT) imaging was used as the reference.

Methods and Results: A total of 673 patients (273 men, 400 women) with known or suspected coronary artery disease and normal ECGs underwent GSPECT Tc99m sestamibi stress tests (exercise stress for 405 patients, pharmacological stress for 268). Post-stress images were gated 30–60 minutes after stress. LVEF was determined using QGS Cedar-Sinai commercial software.

Results were grouped according to type of stress (exercise or pharmacological) and the interpretation of perfusion imaging (normal or abnormal). LVEF was similar after exercise and pharmacological stress in patients with normal (69±7 vs 69±7) and abnormal (61±9 vs 62±10) stress perfusion. LVEF was < 45% (lower limit of normal) in only 7/673 patients (1%).

Conclusions: Normal ECG reliably predicts normal LVEF measured by post-stress GSPECT. Absolute LVEF value is lower in patients with stress perfusion defects.

Key Words: Ejection fraction, ECG, gated SPECT, GSPECT.

LEFT VENTRICULAR SYSTOLIC FUNCTION, commonly expressed as the ejection fraction (LVEF), is an important determinant of prognosis for patients with cardiac disease, and often forms the basis for therapeutic decisions (1, 2). Measurement of LVEF by contrast angiography, echocardiography, radionuclide angiography, magnetic resonance, or gated single-photon emission computed tomography (GSPECT) imaging requires time, technology and professional attention, and may expose patients to radiation.

Correlations between left ventricular function and findings on 12-lead surface electrocardiography (ECG), a readily available and inexpensive test, have been studied for a limited number of patients using contrast angiography or nuclear angiography as a reference standard (3–7). Normal ECG is both consistent with normal left ventricular function and independently predictive of a favorable prognosis (8).

LVEF measurements acquired by GSPECT at the time of myocardial perfusion imaging correlate closely with ejection faction (EF) values derived by other modalities (9, 10). Automated calculation of LVEF by GSPECT is reproducible with relatively little interobserver variation (11).

The purpose of this study was to examine whether a normal ECG at rest predicts normal left ventricular systolic function, as assessed by GSPECT imaging in patients referred for stress test myocardial perfusion imaging.

---

[1] Associate Professor and [2] Assistant Professor, The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Milena J. Henzlova, M.D., Box 1030, The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; Email: milena.henzlova@mssm.edu

Adapted from a Grand Rounds presentation to The Zena and Michael A. Wiener Cardiovascular Institute, Department of Medicine, Mount Sinai School of Medicine, New York, NY, on November 20, 2000, and updated as of March 2003.

Methods

A database of patients referred for GSPECT Tc99m sestamibi stress testing because of known or suspected coronary artery disease with a normal resting ECG was searched over an 18- month period (from 1/00 to 6/01). Of a total of 5,311 patients, 673 consecutive patients with normal rest ECGs were identified (273 men and 400 women). Of them, 405 patients (mean age 59±11 years) underwent symptom-limited treadmill exercise testing, and 268 (mean age 64±13 years) underwent pharmacological stress testing. Medications were given routinely unless the referring physician requested interruption.

A standard 12-lead ECG was acquired at rest for all patients, and was interpreted according to the Minnesota code (12) by cardiologists blinded to the results of perfusion imaging. The only abnormal pattern considered normal for the purpose of this analysis was sinus bradycardia at rates (heart rate ≤ 59 bpm).

Exercise testing was performed according to the Bruce protocol (13), with the heart rate, blood pressure and 12-lead electrocardiogram recorded before, during and after exercise. Exercise was terminated when limiting cardiac symptoms (chest pain or shortness of breath) or fatigue occurred, or when there was greater than a 2 mm horizontal and/or downsloping ST-segment depression measured 80 milliseconds after the J-point over at least three consecutive beats. In patients unable to exercise adequately, dipyridamole (0.56 mg/kg) or adenosine (140 μg/kg for 6 minutes) was infused intravenously.

GSPECT imaging was performed using a dual-head camera (Vertex Plus; ADAC Laboratories, Milpitas, CA) using stop-and-shoot acquisition with 64 stops, 180° arc from right anterior oblique to left anterior oblique, and a 64×64×16 matrix, VXGP collimator. Tc99m sestamibi was injected at rest and at peak stress (same day, single isotope protocol). Image acquisition began 30–60 minutes after tracer injection, and only the post-stress images were gated.

Stress and rest perfusion images were evaluated subjectively and semi-quantitatively by experienced nuclear cardiologists, who were not blinded to the clinical history or resting ECG findings. Imaging results were classified as normal or abnormal. LVEF was determined using commercial software (QGS, Cedar-Sinai, Los Angeles, CA) (13), with 45% considered the lower limit of normal.

Statistical analysis involved the Student t-test for unpaired variables, with significance accepted at the 99% confidence limit (p<0.01).

Results

Patients were grouped according to the type of stress (exercise or pharmacological) and the perfusion imaging results (normal or abnormal). Patients who underwent exercise testing (n=405) were younger (59±1 years) than those who underwent pharmacological testing (n=268 patients, age 64±13 years, p<0.01). Perfusion during stress was normal in 431 patients and abnormal in 242; the LVEF was higher in those with normal perfusion (69±7 vs 62±10%, p<0.001). In patients with normal perfusion, LVEF was no different after exercise than after vasodilator administration (69±7% vs 69±7%, p=ns) (Table 1). LVEF was <45% in 7 of the 673 patients in this cohort (1%), and stress perfusion was abnormal in each of these; 25 patients (3.7%) had an EF <50%. No patient had LVEF <40% (Table 2).

Discussion

Our data indicate that for this group of patients with known or suspected coronary artery disease (CAD), a normal 12-lead ECG pattern correlated well with a normal, or minimally abnormal, LVEF as measured on post-stress

TABLE 1
LVEF (%) According to Type of Stress and Stress Perfusion Findings

Perfusion	Exercise Stress Test (n=405)	Pharmacological Stress Test (n=268)
Normal (n=431)	69±7	69±7
Abnormal (n=242)	61±9*	62±10**

*p = 0.01, **p <0. 01 when compared to normal perfusion.
LVEF = left ventricular ejection fraction.

TABLE 2
Distribution of LVEF Values (n=673 patients)

LVEF (%)	Number of patients (%)
≥50	648 (96.3%)
45–49	18 (2.7%)
40–44	7 (1%)
<40	0

LVEF = left ventricular ejection fraction.

GSPECT imaging. The LVEF is lower in patients with stress-induced perfusion defects than in patients without such defects.

Previous investigators have found that LVEF (measured by contrast ventriculography) was normal in patients with normal ECG at rest, including occasional patients with mild hypokinesis limited to a single wall segment (3). In another study the sum of the R-wave amplitudes in six precordial and two augmented limb leads was used and compared to angiographic LVEF during a sinus beat and during a post-extrasystolic beat. The sum of R waves correlated with the LVEF in both types of beats (4). Among patients with known or suspected CAD and normal resting ECG in the Cardiac Arrhythmia Suppression Trial (CAST) registry (n=4,034), LVEF measured by contrast ventriculography was >50% in 92%, mildly abnormal in 8% and ≤35% in 0.6% of patients (5). More recently, Khan et al. (6) used a 29- point scoring system based on the QRS complex in 391 patients undergoing coronary angiography and contrast ventriculography. LVEF was >50% in 93% of patients with normal QRS complex scores. When the ECG was classified subjectively as normal by cardiologists, the LVEF was normal in 98% of patients.

In 874 patients with suspected CAD but no clinical history of myocardial infarction and a normal ECG, the LVEF measured by resting radionuclide ventriculography (gated blood pool imaging) was >50% in 95% (7). For 1,154 patients with angina pectoris, the five-year and 10-year survival rates (87% and 71%, respectively) were greater for patients with normal baseline ECG than for those with abnormal tracings (71% and 46%, respectively).

Taken together with our observations, these data confirm that a normal resting ECG is associated with good left ventricular function and with a favorable prognosis. To apply these correlations in clinical practice requires a strict definition of ECG normalcy: even minor repolarization abnormalities may have different diagnostic implications. It should also be emphasized that the finding of a normal LVEF does not exclude significant (even multivessel) CAD. Stress perfusion imaging was abnormal in 36% of our patients, many of whom may have harbored epicardial CAD. The absolute value of LVEF was lower in patients with abnormal stress perfusion (Table 1). This finding can be explained by either presence of chronic segmental wall motion abnormalities or by ischemic stunning (or a combination of both mechanisms). GSPECT imaging data were collected beginning 30–60 minutes after stress, and stress-induced ischemic ventricular dysfunction may persist beyond this interval, particularly after exercise (14).

Study Limitations

Using GSPECT imaging, we could not diagnose significant mitral regurgitation, which has both therapeutic and prognostic significance and thus limits the generalizability of our data. Nuclear cardiologists, who reported the LVEF value, were not blinded to the ECG tracings and myocardial perfusion results. However, since the calculation of the LVEF is fully automated, reporting bias is unlikely.

Conclusions

Our findings confirm that a normal surface ECG is associated with a high likelihood of normal post-stress left ventricular ejection fraction determined by GSPECT in patients undergoing stress testing for evaluation of suspected or known coronary artery disease. Additional or repeat use of more sophisticated methods to measure left ventricular systolic function in this group of patients may be unnecessary and associated with the undesirable waste of health care dollars.

References

1. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestiv heart failure. N Engl J Med 1991; 325:293–302.
2. MERIT-HF Study Group. Effect of metoprolol CR/XL in chroni heart failure: metoprolol CR/XL randomized intervention tria in congestive heart failure. Lancet 1999; 353:2001–2007.
3. Swartz MH, Pichard AD, Meller J, et al. The normal electrocar diogram as a predictor of left ventricular function in patient with coronary artery disease. Br Heart J 1977; 39:208–211.
4. Askenazi J, Parisi AF, Freedman WB, Braunwald E. Value of th QRS complex in assessing left ventricular ejection fractio Am J Cardiol 1978; 41:494–499.
5. Rihal CS, Davis KB, Kennedy JW, Gersh BJ. The utility of cli ical, electrocardiographic, and roentgenographic variables the prediction of left ventricular function. Am J Cardi 1995; 75:220–223.
6. Khan MA, Sinha S, Hayton S, et al. A normal electrocardiogra precludes the need for left ventriculography in the asses ment of coronary artery disease. Heart 1998; 79:262–267.
7. O'Keefe JH, Zinsmeister AR, Gibbons RJ. Value of norm electrocardiographic findings in predicting resting left ve tricular function in patients with chest pain and suspect coronary artery disease. Am J Med 1989; 86:658–662.
8. Connolly DC, Elveback LR, Oxman HA. Coronary artery disea in residents of Rochester, Minnesota. IV. Prognostic value the resting electrocardiogram at the time of initial diagnosis angina pectoris. Mayo Clin Proc 1984; 59:247–250.

9. Nichols K, Tamis J, DePuey EG, et al. Relationship of gated SPECT ventricular function parameters to angiographic measurement. J Nucl Cardiol 1998; 5:295–303.
10. Cwajg E, Cwajg J, He ZX, et al. Gated myocardial perfusion tomography for assessment of left ventricular function and volumes: comparison with echocardiography. J Nucl Med 1999; 40:1857–1865.
11. Germano G, Kiat H, Kavanaugh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med 1995; 36:2138–2147.
12. Blackburn H, Keys A, Simonson E, et al. The electrocardiogram in population studies: a classification system. Circulation 1960; 21:1160–1175.
13. Froelicher VF. Manual of exercise testing. St. Louis (MO): Mosby; 1994.
14. Johnson LL, Verdesca SA, Aude WY, et al. Postischemic stunning can affect left ventricular ejection fraction and regional wall motion on post-stress gated sestamibi tomograms. J Am Coll Cardiol 1997; 30:1641–1648.

Cardiothoracic Surgery at The Mount Sinai Hospital

Robert S. Litwak, M.D.

Abstract

Beginning in the early years of the twentieth century, there has been a continuing record of significant contributions made by Mount Sinai physicians to the surgical management of thoracic and cardiovascular pathology. The availability of intratracheal anesthesia, a method developed at this institution, was the *sine qua non* which made it possible for surgeons to perform thoracic, and later cardiac procedures. Of great importance to medicine in general, and surgery in particular, were the investigations of two Mount Sinai physicians that made the transfusion of blood safe, and the modern blood bank a reality. The later contributions of Mount Sinai staff members to the effective employment of open-heart surgery without the use of donor blood, mechanical support of the failing heart, cardiac transplantation, and complex aortic surgery are described.

Key Words: History of cardiothoracic surgery, cardiac surgery, pacemaker implantation, hypothermia, intratracheal anesthesia, blood transfusion, Jehovah's Witness.

Over the years, the contributions of a number of Mount Sinai physicians have been of key importance in the development of thoracic and cardiac surgery. A towering figure was Howard Lilienthal, who began his service here as a junior house staff physician (1886), rose to the distinguished level of consulting surgeon (1922), and went on to become an internationally acclaimed authority on thoracic surgery.

Lilienthal's interest and involvement in developing not only thoracic but also cardiac surgery was apparent from his early years at Mount Sinai. His classic two volume text, *Thoracic Surgery*, was published in 1926 (1). In addition to comprehensive discussions of pulmonary, esophageal and related pathology, Lilienthal devoted four chapters to the management of cardiac and great vessel problems. He described his experience with pericardiostomy (1889), limited excision of pericardial constriction (1923) and management of life-threatening aortic aneurysms (1907, 1914). An extensive section of the book was devoted to the management of pulmonary embolism and described an attempted pulmonary embolectomy performed by Harold Neuhof on a patient who was in profound shock, having recently undergone an abdominal operation (date not stated). The book further reveals Lilienthal's insight in anticipating the role of surgery in the management of cardiac valvular pathology (2):

> The most important heart lesions which may some day come regularly to the surgeon are the aortic stenoses, the mitral stenoses, and possibly stenoses of the pulmonary arteries. Perhaps also some tricuspid contractions may be added to the list of surgical conditions.

Lilienthal described in considerable detail the first successful use of transventricular valvulotomy in the relief of mitral stenosis, which had been performed in 1923 by the distinguished Harvard surgeon, Elliot Cutler. It was clear that Lilienthal also appreciated the potential role of surgery in congenital cardiac and great vessel problems such as patent ductus arteriosus. Lilienthal observed (3), "The anomaly in which surgery promises some hope is that of [ligating a] persistent ductus arteriosus."

Address all correspondence to Dr. Robert S. Litwak, Professor, Department of Cardiothoracic Surgery, Box 1028, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Accepted for publication January 2002.

Other members of Mount Sinai's staff also made contributions of enormous importance to the developing fields of thoracic and cardiac surgery. One of these trailblazers, Charles Elsberg, was responsible for the first clinical application of a method which would effectively deal with the one overriding deficiency which, above all others, had delayed any substantive progress in the field — the lack of a simple and predictable method of establishing and maintaining adequate pulmonary ventilation when the thorax was open and the lung exposed. Elsberg was impressed with the 1909 report of two Rockefeller Institute physiologists, Meltzer and Auer, who experimentally demonstrated the efficacy of a simple apparatus which could maintain expansion of the lungs while administering anesthesia employing a method of intratracheal insufflation, thereby permitting safe transpleural exposure (4). In February of the following year, Elsberg (who later would distinguish himself as Mount Sinai's chief of Neurosurgery) utilized the Meltzer and Auer concept for the first time in a clinical open-chest procedure. Employing an apparatus he himself had constructed, Elsberg administered intratracheal anesthesia to a patient being operated on by Lilienthal for a lung abscess (5). In the next two years more than 400 operations were performed employing the Elsberg system, and within five years the method was employed throughout the world. Almost a half-century later, the distinguished thoracic surgeon, Evarts A. Graham, observed (6):

> There is no doubt that this simple device has been one of the most important foundation stones upon which the structure of modern chest surgery has been erected. [However] in spite of the great importance of this simple method of avoiding the collapse of the lung it was used very little before the First World War largely because there were very few surgeons prepared to undertake intrathoracic operations, in addition to the fact that the diagnosis of intrathoracic disease was far from accurate [since] the Coolidge tube which made the X-ray examination of the thorax feasible was not invented until 1917.

One can hardly conceive of a patient undergoing major thoracic or cardiac surgery today without the immediate availability of carefully typed, cross-matched blood. Two distinguished members of Mount Sinai's staff helped make the modern blood bank a reality. Reuben Ottenberg (who later would be recognized as one of this institution's outstanding physician investigators) not only performed the first blood transfusions in New York City (1907 and 1908) but also — utilizing Landsteiner's description of blood groups — was the first to employ the practice of typing and cross-matching of blood donors and recipients (7). Another Mount Sinai physician, Richard Lewisohn (who rose from adjunct to attending surgeon), introduced the use of citrate as an anticoagulant in donor blood, thereby making it possible for blood to be stored. Thus was born the basis for the modern blood bank (8, 9).

Early Experience with Extracardiac Surgery at Mount Sinai

In 1940, after the seminal report of Robert E. Gross of the first successful ductal ligation (10) and two years after John Strieder's report of an unsuccessful attempt to obliterate a ductus complicated by bacterial endarteritis (11), Arthur Touroff, a member of the Mount Sinai surgical staff, reported the first survivals of two of four patients who underwent ductal obliteration in the presence of active *Streptococcus viridans* infection (12, 13). In that preantibiotic era, it is of importance that the blood cultures of one of the survivors immediately became and remained sterile following ductal division. In the second survivor, bacteremia was reported as being significantly reduced. A paper published by Mount Sinai's Cardiovascular Research Group revealed that it was also Touroff who, following the monumental report of Blalock and Taussig (14) describing the efficacy of systemic pulmonary artery shunts in the management of cyanotic heart disease — successfully performed the first shunt procedure at this institution, on a five-year-old child with complex cyanotic congenital heart disease, in April of 1949 (15).

Cardiac Surgery after the Second World War

Closed Intracardiac and Extracardiac Surgery at Mount Sinai: The Early Years

The end of the Second World War coincided with an enormous burst of interest throughout the surgical world in developing operative approaches to congenital and acquired cardiac and great vessel pathology. Undoubtedly, the stimuli for this heightened interest were (a) the success of Gross and Blalock in the United States and Crafoord (Sweden) in the management of an increasing number of extracardiac congenital cardiovascular lesions, and (b) the brilliant success achieved during World War II by Lt. Col. Dwight E. Harken, who had performed 134 operations in which foreign bodies were removed from the heart and great vessels without any mortality (16). Harken had demonstrated that well planned and skillfully executed cardiac and thoracic operative procedures could be accomplished with a high degree of success. The multiple elements underlying that achievement — so long in coming — were at last at hand: well-controlled endotracheal anesthesia, the ability to replace blood loss with whole blood, a skilled surgical team, meticulous postoperative care by experienced nurses and physicians in areas which would now be identified as intensive care units, and finally, the newly available antibiotic penicillin. Only three years after the end of the war (1948), Harken in Boston, Charles Bailey in Philadelphia and Russell Brock in London — each unaware of the others' efforts — independently and convincingly demonstrated the efficacy of surgical relief of severe mitral stenosis. Predictable intracardiac surgery having become a reality, Robert Nabatoff of the Mount Sinai surgical staff initiated a highly successful series of surgical enlargements of the stenotic mitral orifice (commissurotomy) in 1951, employing the techniques recently described by Bailey, Harken and Brock. During this same period, two other members of the Mount Sinai surgical staff, Irving Sarot and Mark Ravitch (the latter having been recruited from Johns Hopkins as Mount Sinai's first full-time director of Surgery), also performed mitral valve operations as well as correction of congenital cardiovascular lesions, including ligation of the patent ductus and resection of a localized, severely narrowed area (coarctation) of the thoracic aorta.

Open-Heart Surgery at Mount Sinai: Early Experience

The first open-heart surgery (OHS) effort at The Mount Sinai Hospital was initiated by Ivan Baronofsky, who had been recruited as director of Surgery (in 1957) from the University of Minnesota (UM), one of the two institutions in the world which were actively involved in clinical OHS at that time (the other being the Mayo Clinic). Having witnessed the clinical success of C. Walton Lillehei and his UM colleagues, who employed a pump and oxygenating unit which was relatively simple, inexpensive and disposable, Baronofsky — upon his arrival at Mount Sinai — promptly initiated an aggressive canine experimental laboratory effort with the UM system, the goal being to begin clinical work as soon as both a reliable pump-oxygenating system and support staff could be established. To accomplish this, he assigned three Mount Sinai surgical residents to various laboratory tasks: Isadore Kreel would perform the surgery, Lawrence Zaroff would run the pump-oxygenator, and David Kavee would be responsible for performing a myriad of other technical chores. After five months of intensive effort involving approximately 200 canine OHS operations employing the Lillehei UM system, two of the residents, Kreel and Zaroff, spent one week at the UM, where they observed all OHS cases performed during that week and were updated on the entire UM experience. Upon their return to New York, Mount Sinai's clinical OHS program was initiated by Baronofsky in January of 1958, with the successful repair of an atrial septal defect in a ten-year-old boy. Following this first successful case, approximately 100 open cardiac operations were performed with an operative procedure scheduled for each Tuesday. Most of the cases involved repair of atrial septal defects, with a smaller number undergoing repair of ventricular septal defects. According to Kreel (who supplied the writer with all of the details of that period), each case was a "logistical nightmare," since the protocol at that time required 20 units of fresh heparinized blood to be drawn on the morning of operation. The patient did not enter the operating room until the required number of blood units were confirmed to be immediately available. Since a cardiac surgical recovery room did not exist at that time, a small area adjacent to the old Guggenheim operating rooms (currently a reception area for patients scheduled for ambulatory surgical procedures) was utilized for immediate postoperative care with surgical residents in constant attendance throughout the night on each case.

Upon Baronofsky's departure from Mount Sinai in March of 1960, an administrative decision was made to discontinue all OHS efforts until a new surgical director and staff could be recruited.

The Division of Cardiothoracic Surgery: The Early Years

In 1961, one of the important early tasks of the newly appointed full-time director of

Surgery, Allan Kark, was the establishment of a Division of Cardiothoracic Surgery (CTS), with an experienced staff which would re-establish the OHS effort and develop strong teaching and research programs. Within months of Kark's arrival, Robert Litwak was appointed director of the newly established Division of Cardiothoracic Surgery. He and his talented colleague, Howard Gadboys, began their work at Mount Sinai in July of 1962. Litwak undertook development of a strong clinical program which sought to integrate both the cardiac and the well-established general thoracic surgical efforts, thereby providing the basis for a formal CTS residency teaching program. Both Litwak and Gadboys shared clinical cardiac surgical responsibilities, and the latter also undertook primary responsibility for development of a research program that would initially focus on study of pathophysiologic events associated with bypass of the heart and lungs (cardiopulmonary bypass) with a mechanical pump-oxygenator exchange device (17, 18).

After a hiatus of two and a half years, open-heart surgery (OHS) began again on August 15, 1962, with the performance of a pulmonary valvotomy in a six-year-old child. In the first twelve months following re-establishment of the OHS program, an average of two open cardiac procedures were performed each week, predominantly on adult patients with acquired mitral and aortic valvular heart disease and on children with various congenital cardiac and vascular malformations.

A number of administrative decisions made by the hospital were of key importance in the re-establishment of an OHS effort at Mount Sinai. A dedicated operating room fully equipped for the conduct of open-heart surgery was established, with six experienced nurses assigned full time to the program. Immediately adjacent to the operating room there was space for both a biochemical laboratory and a "pump room" (where the heart-lung machine would be assembled and disassembled). Two experienced perfusionists (Bennett Mitchell and Phillip King) were recruited to run the heart-lung machine. Additionally, two physiological-biochemical technicians were recruited and assigned on a full-time basis to the cardiac operating room and recovery areas. Of great importance was establishment of a well-equipped, two-bed CTS Intensive Care Unit (CTSICU) with state-of-the-art monitoring equipment and staffed with six experienced nurses who delivered excellent around-the-clock care to fresh postoperative OHS patients.

Cardiothoracic Surgery Residency Program

With re-establishment of an active cardiac surgical effort and the presence of a substantial volume of patients requiring a variety of non-cardiac thoracic surgical procedures, a two-year CTS residency program was immediately established. B. George Wisoff, a brilliant young surgeon (who would later distinguish himself as chief of Cardiac Surgery at the Long Island Jewish Medical Center) was the first CTS resident. Once the CTS residency program was operational, a site visit was made by a group representing both the American Medical Association's Accreditation Committee for Graduate Medical Education (ACGME) and the American Board of Thoracic Surgery (ABTS). As a result, a two-year training program was given formal approval. The initial approval stipulated that only one CTS house officer could be trained in each two-year period. Fortunately, second- and third-year general surgical residents augmented the house staff with three-month CTS rotations.

The progressive increase in patient volume and the necessarily limited exposure of a single CTS resident to a broad spectrum of both pediatric and adult thoracic and cardiac cases requiring surgery prompted a second request to and subsequent approval by the ACGME and ABTS (in 1975) for augmentation of the CTS resident staff to two house officers. The additional resident position permitted the first-year resident to focus primarily on general thoracic surgical problems and the second-year resident, as the CTS Chief Resident, to focus on management of patients requiring cardiac surgery. In reality, however, the ever-expanding cardiac surgical volume often resulted in the first-year thoracic resident suddenly being spirited away to scrub in as an assistant on a complicated cardiac surgical case. Thus, the goal of a predictable and continuing experience in non-cardiothoracic surgery still was not being met. Once again, the ACGME and ABTS were approached (in 1983) with a request to lengthen the CTS residency from two to three years. While the request was approved, we were to learn later that it had been done with considerable ambivalence since a number of committee members had pointedly indicated that no other institution had expressed the need to lengthen its CTS residency because of perceived limitation of general thoracic surgical resident experience. However, it was gratifying to note that within the next five years a substantial number of institutions with approved CTS residencies had elected to extend their programs to three years.

Beginning in the early 1970s and continuing for a number of years, CTS residents rotated through the Bronx Veterans' Administration Hospital to augment their experience in a wide variety of thoracic problems, particularly pulmonary and esophageal disease. Under the knowledgeable guidance of the chief of Thoracic Surgery, Hideki Sakurai, and the chief of Surgery, A.J. McElhinney, the experience was a consistently rewarding one.

Nursing and Support Staff

Nurse Clinicians

The steadily increasing patient volume soon made it apparent that CTS residents, who were frequently in the operating room for many hours, needed help in providing and coordinating perioperative patient care. It was for this reason that a CTS nurse clinician program was established in 1964. These individuals were highly qualified nurses who almost invariably had prior CTSICU experience. Their responsibilities included making daily rounds with the CTS staff and communicating any concerns or decisions made at rounds with cardiologists and consultants, making certain that the necessary myriad of management "paperwork" had been completed, and taking the time to discuss at length with both patient and family any concerns that might have arisen concerning projected care plans. The program proved to be highly successful and remains an important CTS operational component.

Physician Assistants

In addition to nurse clinicians, certified physician assistants (PAs) have played a significant role in patient management at Mount Sinai since 1978. The PA support concept was originally established at Duke University in the 1960s because of the sharp limitation of approved surgical resident positions by accrediting agencies. With college backgrounds supplemented by two years of formal lectures and supervised medical and surgical patient care experience in accredited programs, PAs are approved to assist CTS surgeons in the operating room and carry out many of the time-consuming tasks previously assigned to residents. Since recruitment of the first PA more than 20 years ago, there has been a gradual increase in the number of CTS PAs (currently 14), a reflection of the importance and effectiveness of these professionals in providing thoughtful patient care.

Bioengineers

The frequent need to develop new instrumentation for research or clinical purposes made it essential that there be close collaboration of CTS staff with bioengineers. In 1966, informal discussions between CTS staff and members of the Artificial Organs Research Laboratory (AORL) of Columbia University concerning investigative areas of mutual interest led to the establishment of a formal relationship, which was recognized with appointment of the AORL director, Edward F. Leonard, Ph.D. (professor of chemical engineering at Columbia University) as lecturer in surgery. This relationship led to the establishment of a fruitful collaborative laboratory research effort (see later discussion).

In 1971, having learned that studies employing on-line computerized analysis of cardiac and pulmonary variables being conducted by John J. Osborne (director, Institute of Medical Sciences at the Presbyterian Medical Center, San Francisco) facilitated postoperative management of critically ill cardiac surgical patients, Roy Jurado (associate professor of Surgery) spent a year working with Osborn and colleagues on this project. Impressed with the efficacy of the system, Jurado and three CTS bioengineers (Richard A. deAsla, Hillard Fitzkee, and Byong Min) constructed a bedside sensing and data acquisition unit at the Institute of Medical Sciences (IMS). The unit was then carefully moved to the CTSICU at Mount Sinai and connected via leased long-distance telephone lines to an IBM 1800 digital computer located in the IMS. On-line real-time computerized surveillance studies of cardiac, hemodynamic and pulmonary variables and parameters carried out by Jurado and colleagues documented for the first time that computerized surveillance could significantly reduce sudden, unexpected life-threatening events in postoperative cardiac surgical patients (19). The data were sufficiently impressive to Mount Sinai administrative staff that they approved funds which permitted full computerization of the newly constructed eight beds located in the old Guggenheim Pavilion.

Two bioengineers, Anthony Benis and Robert M. Koffsky (whose initial involvement with CTS was as members of the AORL conducting collaborative research at Mount Sinai), later became full-time members of CTS and made a number of major contributions over the years. After collaborating with CTS staff for several years Benis, with more than ten years of bioengineering background, elected to seek a degree in medicine and graduated from the Mount Sinai School of Medicine in 1976. His medical career blossomed and he currently is director of the CTS Intensive Care Unit. Koffsky, having left the AORL for a relatively brief but productive experience in the research division of a West Coast pharmaceutical firm, was persuaded to return to CTS in 1976 to coordinate instrumentation development for the research laboratory, the CTS operating rooms and the new twelve-bed CTSICU in the Lucy Moses Cardiothoracic Center in the recently completed Annenberg Building.

Growth of the Cardiac Surgical Program: 1962–1985

As a consequence of collaboration of pediatric cardiology and adult cardiology colleagues, the volume of cardiac operations steadily expanded over the years. All patients referred for surgery underwent diagnostic hemodynamic studies by the cardiac catheterization team (directed by Alvin Gordon). There was also excellent angiographic input by Murray Baron of the Department of Radiology. The pediatric cardiology effort was directed by Leonard Steinfeld, who was later joined by Rica Arnon. Both physicians performed diagnostic catheterization studies in children. The adult cardiology group was directed by the distinguished Charles Friedberg, whose conservatism was legendary when considering patients for cardiac surgery. Nonetheless, many members of the Department of Medicine and the Division of Cardiology regularly referred patients for cardiac surgery.

Surgery for Congenital Cardiac and Great Vessel Problems

In the 1960s and 1970s, OHS for severe congenital cardiac cases in the first year of life was still in the development stage. Neonates and infants with severe cyanotic heart disease (such as tetralogy of Fallot) — rather than undergoing open cardiac correction at that young age — underwent palliative surgery (Blalock-Taussig operations) which increased pulmonary blood flow, with reduction of cyanosis, and improved the general condition of the child. Similarly, infants with life-threatening large ventricular septal defects underwent pulmonary artery banding (partial occlusion), which reduced excessively high blood flow to the lungs and thereby improved the child's stability. Only a decade later would open-heart corrections of the above lesions be performed in the first year of life.

Valve Repair and Replacement

The availability of OHS methodology permitted Mount Sinai surgeons the option of performing closed mitral commissurotomy in patients with favorable (non-calcific, non- regurgitant) rheumatic mitral stenosis. At operation, if necessary, the surgeon could immediately switch to the open-heart approach. One of the early reports of the method was published by Mount Sinai CTS staff in 1965 (20).

With the development of caged ball valve prostheses by Albert Starr and engineer Lowell Edwards in the early 1960s (21) patients with otherwise uncorrectable, far-advanced mitral and/or aortic valve pathology could now undergo replacement of one or more valves. The first patient at The Mount Sinai Hospital to undergo implantation of a Starr-Edwards mitral valve was operated upon in May of 1963. In August of that year the first Starr-Edwards aortic valve prosthesis was implanted. The first combined mitral and aortic valve replacement performed with these prostheses was also carried out in August 1963.

While improvements continued to be made in mechanical prosthetic valves over the years, the disturbing frequency of thromboembolic complications required that all patients be maintained permanently on warfarin, an effective anticoagulant. While capable of reducing the potential of thromboembolism, warfarin imposed the equally threatening possibility of intracerebral or other vital organ bleeding.

A welcome addition to the surgical armamentarium was the development (in the mid-1960s by Carpentier and colleagues in Paris) of stent-mounted, aldehyde-treated aortic porcine xenografts, which offered the hopeful possibility of avoiding the need for indeterminate anticoagulation (22). The first commercially available, formalin-fixed stented porcine xenograft (Hancock Laboratories) was implanted in the mitral position at The Mount Sinai Hospital in November 1968. Over the next two years, 59 patients underwent single or multiple-valve replacements with these bioprostheses. Unfortunately, initial enthusiasm for the porcine xenografts was tempered by early leaflet failure. Within thirty-six months, every one of the implanted, formalin-fixed bioprostheses had developed evidence of significant incompetence which required their replacement with a mechanical (Starr-Edwards) prosthesis. Fortunately, all patients who had undergone initial bioprosthetic implantation survived their subsequent removal and replacement with a mechanical prosthesis. In recent years, as a result of improved methods of leaflet preservation, bioprosthetic valve replacement is again being performed in appropriately selected patients. Women of childbearing age in regular cardiac (normal sinus) rhythm and elderly patients with aortic valve pathology are candidates for bioprosthetic valve replacement, since anticoagulation can be discontinued several months after operation with minimal risk of thromboembolism and the implanted valves can be expected to remain competent for approximately a decade.

Coronary Artery Bypass

Following demonstration by Favaloro and colleagues at the Cleveland Clinic (1968) (23) of the efficacy of coronary artery bypass grafting (CABG) utilizing reversed saphenous vein segments in the management of severe coronary artery disease, many institutions throughout the world promptly began aggressive CABG programs. Unfortunately, referral of patients for CABG surgery at Mount Sinai was quite slow for a number of years following Favaloro's report, presumably because persuasive information which clearly documented improved longevity, reduced potential of future myocardial infarctions, etc. had not yet been published. Indeed, the first CABG procedure at this institution was performed in 1971, but the volume still remained small. Only after documentation of the efficacy and improved long-term patency of internal mammary artery grafts by George Green (24) did the CABG volume significantly increase. It is pertinent that Green demonstrated the clinical efficacy of anastomosis of the internal mammary artery to the left anterior descending coronary artery, employing an operating microscope, originally developed by a young surgical investigator, Julius Jacobson II (25), who would later become Mount Sinai's distinguished director of Vascular Surgery. Characterized by the late physiologist and historian, Julius Comroe (26), as "one of the great cardiovascular advances . . . ," the microvascular surgical methods and principles established by Jacobson have become the bedrock underlying successful performance of a wide variety of cardiovascular and other surgical procedures performed today.

From its inception, the CTS CABG program was superbly directed by Salvador Lukban and, later, by Manuel Estioko and Bruce Mindich. Estioko's employment of a "no blood" approach in the management of Jehovah's Witnesses (whose religion absolutely forbids use of donor blood or blood products) referred for CABG or other cardiac surgery quickly led to Mount Sinai being designated as a regional referral cardiac surgical center for this religious group (27).

Permanent Pacemaker Implantation

The development of permanent implantable cardiac pacemakers in the early 1960s sharply improved the dismal outlook of patients with complete heart block. The first permanent pacemaker was implanted by Howard Gadboys and CTS resident, George Wisoff, in an elderly patient in September 1962. In the early years (prior to the development of permanent transvenous pacing methods), permanent pacemaker implantation required a formal thoracotomy. There was close collaboration with members of the cardiology catheterization team (directed by Alvin Gordon) who would insert a preliminary temporary transvenous catheter electrode into the patient's right ventricle to attain immediate cardiac pacing. With the patient anesthetized, the CTS team would open the chest, expose the heart and insert permanent pacing electrodes directly into the left ventricle. The pacing electrodes would then be connected to a generator to begin the pacing. Although the early pacing methods unquestionably improved the outlook for patients, accumulating experimental and clinical evidence clearly suggested significant physiologic advantages if atrioventricular synchrony could be maintained. The fortunate development of a fully implantable permanent synchronous pacing unit in 1963 permitted CTS staff to begin implantation of such units that same year. While clearly advantageous from the physiologic standpoint, the surgical approach was somewhat more extensive, because both the left atrium and left ventricle required exposure for electrode implantation. This could only be accomplished by employing a large thoracic incision in an anesthetized patient.

A major advance which eliminated the need of thoracotomy for pacemaker implantation was the development by several investigators of permanent transvenous endocardial pacemaker catheter lead and generator systems. Implantation required only local infiltration anesthesia in an awake patient. The first procedure of this type was performed at Mount Sinai by CTS in 1966. As in the early pacemaker experience, Gadboys continued to direct the program in collaboration with Salvador Lukban, a gifted resident who would later become a member of the CTS attending staff. Over subsequent years, the program was directed by Estioko and, later, by Jorge Camunas. In recent years, Jan Galla of CTS has joined Camunas in managing the steadily increasing volume and spectrum of pacemaker implantations. Over the years, the program has been fortunate to have magnificent nursing collaborators, initially Yael Duvduvani, R.N. and, in recent years, Unsoon Shagong, R.N.

Progress in the management of heart block and other electrophysiologic distortions in the three decades since the early pacemaker implantations has been extraordinary. The pacemaker program has grown steadily, with the annual implant volume averaging 200–230 patients. Each patient requires arrhythmia analysis and implantation of a pacemaker which deals with the specific conduction problem. The pacemaker group also has substantial experience in the effective management of several types of life-threatening ventricular arrhythmias, employing an implantable cardiac defibrillator (ICD) device which, having detected the problem, immediately shocks the heart to reestablish normal cardiac rhythm. The effort has been a collaborative one involving CTS surgeons and the Division of Cardiology's excellent electrophysiology group (directed by J. Anthony Gomes) in both arrhythmia diagnosis and operative management. Each year more than 75 patients receive these literally life-saving ICD units.

Mechanical Support of the Failing Heart

The urgent need for pump assistance for the failing heart had been appreciated since the early days of OHS. The first system employed by many cardiac surgical groups was the intra-aortic balloon pump (IABP). The IABP operational concept is based on the arterial counterpulsation principle developed in the early 1960s (28). The pump utilizes a rapidly inflatable and deflatable balloon which is positioned in the aorta just beyond the origin of the carotid arteries (which supply blood to the brain). Utilizing the electrocardiogram, the balloon is timed to deflate immediately preceding onset of left ventricular (LV) contraction, thereby reducing the energy-consuming work that the LV must perform in ejecting blood into the aorta. During the succeeding cardiac diastolic phase (when the LV is being refilled from the left atrium with oxygenated blood coming from the lungs), the IABP suddenly inflates, causing the arterial pressure to rise. The overall result is an improvement in hemodynamic stability and reduced work stress on the heart.

First utilized at Mount Sinai in 1972, the IABP was deployed in a patient with advanced cardiac dysfunction undergoing OHS whose post-repair low cardiac output did not permit discontinuance of the heart-lung machine. The IABP successfully stabilized the hemodynamic state of the patient so that the heart-lung machine could then be discontinued. The patient recovered satisfactorily and was subsequently discharged.

In later years, development of a percutaneous method of IABP insertion proved to be of great importance in the cardiac catheterization laboratory and coronary care unit when patients suddenly manifested cardiac ischemia as indicated by altered electrocardiogram or by angina. In these patients, the IABP was effective in promptly alleviating the ischemic episode and restoring hemodynamic stability. In the early years of IABP use at Mount Sinai, Roy Jurado (associate attending surgeon) and Richard DeAsla (senior CTS bioengineer) had been responsible for the direction and supervision of the highly effective IABP support program.

In the 27 years since the IABP was first employed at this institution, it is estimated that the system has been employed in approximately 2,500 patients and continues to represent the first line of defense in managing severe cardiac dysfunction.

A second circulatory support system, the Left Heart Assist Device (LHAD), was developed at Mount Sinai by CTS investigators and subsequently utilized by many cardiac surgical groups. The LHAD was first utilized at Mount Sinai in 1973 in a critically ill patient with low cardiac output following cardiac repair. Despite prior use of the IABP, this patient still could not be separated from the heart-lung machine (29). The system consisted of special biocompatible silicone elastomer cannulae which were connected to a pump. The first LHAD cannulae which were employed clinically were designed at Mount Sinai and fabricated by Robert Koffsky, an extraordinarily talented bioengineer who was a member of the CTS staff. One cannula was sutured to the left atrium (LA), the chamber which receives oxygenated blood from the lungs and delivers it to the LV. The other cannula was sutured to the aorta (beyond the LV).

In operation, the LHAD offered the dual advantages of (a) decompressing and unloading the failing LV of blood which it was unable to eject and (b) significantly augmenting systemic arterial blood flow and pressure, to restore and sustain adequate performance of all organ systems until the heart had recovered sufficiently to permit discontinuance of mechanical support. An additional advantage of the support system was that after discontinuance of the LHAD, the highly biocompatible cannulae could be occluded by precisely fitting obturators, without the necessity of reentering the chest. Results in the desperately ill patient group requiring LHAD support revealed that approximately one in three recovered sufficient cardiac function to permit LHAD separation, subsequent hospital discharge and long-term survival. Although other mechanical systems have replaced the LHAD in recent years, it is pertinent that the latter was one of the earliest cardiac support systems to be described and utilized clinically throughout the world.

The Cardiothoracic Surgical Research Laboratory: 1962–1985

With establishment of the Division of Cardiothoracic Surgery in July of 1962, an immediate effort was made to develop a vigorous research program. A CTS animal research facility was provided by the institution, on the seventh floor of the Atran research building. The laboratory was directed by Gadboys with support staff consisting of an experienced veterinarian, Howard Shiang, Wiltrud Berger (who later would marry Gadboys), and a research fellow, Junichi ("John") Ishiguro. The focus of the investigations centered upon exploration of problems accompanying the use of the heart-lung machine which were believed to contribute to both mortality and morbidity.

A major concern of the laboratory was to better understand factors underlying the frequently observed, isotopically measured hypovolemia after cardiopulmonary bypass (CPB), a volumetric distortion commonly observed in the early days of open-heart surgery, when gravimetrically measured blood loss was replaced volume for volume in an attempt to rigidly maintain blood balance (normovolemia) during the course of CPB. On clinical grounds, it was apparent that attempts to maintain normovolemic conditions were accompanied by hypotension. When the extent of the hypovolemia, measured isotopically, was reversed by the administration of additional blood, the patients did far better. What was the basis of the hypovolemia? Gadboys and colleagues hypothesized that as with canines which were suspected of developing severe, frequently lethal reactions when mixed units of homologous blood were utilized to prime the CPB machine humans might be experiencing a similar, albei less severe, reaction manifested by sequestration of a portion of both the formed components of the blood (red, white cells and platelets) as well as plasma.

Supported by a grant from the Nationa Heart Institute, a large number of canine investigations were carried out, which clearly incriminated homologous blood as the etiologic factor in producing these reactions (17). Subsequent studies in humans proved to be similar to those observed experimentally and were the basis for important changes in the conduct o clinical OHS: redesign of the heart-lung machine to permit reduction of the priming volum and use of electrolyte solutions to replace an dilute the homologous blood needed to prim the heart-lung machine (18). Application c these two principles made it possible for OH to be performed without use of homologou blood. This approach was brilliantly employe by Denton Cooley (Texas Heart Institute) whe he, for the first time, successfully performe OHS on a Jehovah's Witness, whose religiou tenets forbid the use of homologous don blood for blood products (30).

Another major area of study evolved fro this discovery that thromboembolism was problem when any type of extracorporeal circulatory support system was employed. Th thrombotic buildup (with ultimate emboliz tion) was believed to be the result of a numb of critical factors, one of the most importa being the foreign plastic and metallic surfac of the devices which were in constant conta with the circulating blood of the patient. Although the patient's blood was anticoagulated with heparin, thromboembolic complications still occurred. Beginning in 1966, CTS investigators, in collaboration with engineering faculty from the Columbia University Artificial Organs Research Laboratory, initiated a series of National Institutes of Health (NIH)-supported investigations which sought to identify factors provoking the thrombotic process. It was hoped that comprehensive understanding of these factors would provide a basis for subsequent investigation of pharmacological agents and new polymeric and other thromboresistant materials which offered promise of effectively blunting thrombus generation. Over the course of a decade of exhaustive study, no clear determination of factors which were operative in initiating the clotting process on foreign surfaces could be identified. Rather, the evidence was persuasive that thromboresistance probably was determined by an environment. It was concluded that while the physical properties of the blood-contacting surface of a test material did play a significant role in determining the potential for thrombus generation, at least four other factors were involved: the hematologic variables present in a given patient, flow geometry, flow rate and the amount of time which the patient's blood was exposed to a test material (31). These studies and those conducted in many other centers, while providing much useful information, failed to find a single "magic bullet" which would effectively solve the thromboembolism problem. In the 30 years which have elapsed since initiation of the investigation, many advances have been made in heart-lung machine design and mechanical circulatory support systems. While the incidence of thrombus buildup and embolization has been reduced, actual elimination of the problem still eludes us.

Division to Department: 1985 and Beyond

Randall Griepp became chief of the Division of CTS in August 1985. The circumstances relating to his recruitment are of some historical interest. In the preceding year a multi-departmental conference group of faculty convened by James Glenn (dean of the medical school and CEO of the medical center), had recommended that the institution undertake a broad transplantation effort, one of a number of areas being cardiac transplantation. Circumstance — that mother of opportunity — immediately brought to Litwak's mind the name of Griepp. Litwak had no clinical experience with the many challenges of cardiac transplantation, whereas Griepp had years of transplantation experience, having been both student (cardiac resident) and, thereafter, colleague of the veritable "father" of cardiac transplantation, Norman Shumway, at Stanford University Medical Center. Having been chief of the Division of CTS for 23 years, Litwak viewed the opportunity to recruit Griepp as a propitious time for a change of leadership.

Griepp's arrival at Mount Sinai opened a new era in cardiac surgery. He was able to persuade his former trainee and subsequent colleague, M. Arisan Ergin, to join him. As Griepp's trusted "right hand," Ergin quickly demonstrated his brilliance as surgeon, investigator, scholar and teacher, the totality of personal qualities which epitomize a superb surgical scientist. The steadily increasing cardiac surgical volume necessitated recruitment of additional CTS faculty over the next few years. Each physician was given primary oversight responsibility for a specific program. With rare exception, these young surgeons who had trained under Griepp were outstanding.

Division to Department

Within several years after Griepp had assumed leadership of the division, and in recognition of the progressive clinical growth and academic impact of the CTS effort, the recommendation by the chairman of the Department of Surgery (Arthur Aufses) that CTS be elevated to departmental status was approved by the Board of Trustees. The excellent general thoracic surgical effort was given full divisional status and continued to be directed initially by Paul Kirschner, later by Steven Keller, and more recently by Paul Waters, all of whom were distinguished in different areas of thoracic surgery.

Expanded Clinical Program

From the outset, it was apparent that Griepp intended to develop a multifaceted CTS program which included not only a cardiac transplantation effort, but the complete spectrum of cardiovascular surgery: the management of life-threatening aortic aneurysms and dissections, complicated valvular and coronary artery problems (which frequently coexist) as well as the broad range of pediatric cardiovascular lesions, particularly in neonates, in whom open cardiac corrections had become feasible and were being performed with increasing frequency.

In all of these endeavors Griepp planned on utilizing a method — hypothermia — which he had employed for almost two decades. His seminal investigative efforts had provided much of the solid basis which permitted its clinical use in complex open-heart surgery.

Hypothermia and Total Circulatory Arrest

Experiments initially reported a half century ago that hypothermia potentially would permit direct vision intracardiac surgery. The reduction of body temperature and metabolic activity of the brain and other vital organs has been extensively investigated and utilized clinically by Griepp and colleagues. They were the first to describe the use of hypothermia to protect the heart to permit a safe period during which the heart could be arrested (by cross-clamping the ascending aorta) to permit repair of complex congenital cardiac defects in infants and children (32). Griepp subsequently utilized the same principle to facilitate correction of complex cardiac and aortic lesions in adults. He utilized the heart-lung machine with a heat-exchanging device to precisely cool the patient's blood to sufficiently low temperature levels, thereby permitting the entire circulation to be totally arrested for approximately 45 minutes without overt damage to the brain and other vital organs. Griepp's successful experience with hypothermia and total circulatory arrest (HCA) in infants and children was most encouraging. He than adapted the method to resection and replacement of aneurysms and dissections of the aortic arch (33). His impressive results with the procedure represented a major contribution, since prior to publication of the Griepp HCA technique, the results of resection of the aortic arch had been dismal. The relative ease of the approach to lesions of the aortic arch led to adoption of the Griepp HCA method by other surgeons, with prompt improvement in their survival figures.

With broadening experience, all groups employing HCA found it occasionally necessary to exceed the generally agreed upon safety limit of 45 minutes. Although significant and prolonged brain damage in these cases fortunately was relatively uncommon at Mount Sinai, the experience provided the impetus for exploration of methods which hopefully would protect the brain during necessarily more prolonged periods of HCA. Funded by a multi-year grant from the National Heart, Lung and Blood Institute of the NIH, Griepp and colleagues developed experimental and clinical data which indicated that considerable residual metabolic activity of the brain could be demonstrated at temperatures previously considered to be sufficiently low to safely permit establishment of a period of circulatory arrest. They concluded that the previously considered "safe period" of HCA (45 minutes) was dangerously too lengthy. Moreover, they demonstrated that significantly better cerebral protection could be maintained, particularly during longer periods of HCA (beyond 45 minutes), with substantially lower blood temperatures (34–37). These and a number of other important technical details developed in the laboratory and subsequently utilized clinically by the Mount Sinai CTS group have been widely accepted and are now employed by cardiovascular surgeons throughout the world.

Aortic Aneurysms and Dissections

The number of patients with life-threatening aortic aneurysms or dissections referred to CTS as possible surgical candidates has resulted in the program being one of the largest in the United States. This program, currently approximately 2,500 patients, has included those requiring emergency surgery because of aneurysm rupture and those undergoing elective operation who, on periodic examination, had been found to have either rapid aneurysmal enlargement or a number of other significant risk factors (chest pain, chronic obstructive pulmonary disease, older age, and poorly controlled hypertension) highly suggestive of impending rupture.

In view of the increased operative risk in the presence of rupture, a prospective study o the natural history of patients with thoraci aneurysms was initiated in 1988 to provide more rational basis upon which appropriate timing of surgery (i.e., pre-rupture) could be made Conducted by Griepp, Ergin, Galla and colleagues, the study involved all aneurysm patients whose clinical condition had no prompted immediate surgery when first see (38–41). By comparison of sequential aorti changes in computer-generated, three-dimensional reconstructions of serial computed tomographic (CT) scans (a method developed b CTS bioengineer, Richard deAsla), the patter of aneurysmal enlargement could be precisel evaluated over time. While quite obviousl surgery was advised for all patients with rapi aneurysm enlargement, a key aspect of the study was the fact that the investigators also were able to derive an equation which could estimate a patient's annualized probability of rupture based upon both the rapidity of aneurysmal enlargement and the non-dimensional risk factors described above. Thus, these sequential studies made it possible to delay surgery with relative safety until such time as the data clearly documented a pre-rupture state. Following publication of the investigation, this equation was widely accepted by cardiovascular surgeons as a rational means of operative timing in all patients presenting with thoracic aneurysms.

The respect for the many contributions made by CTS faculty in the management of thoracic aneurysm is reflected in the consistent attendance of more than 1,000 surgeons at each of the sponsored Aortic Surgery Symposia held every other year since 1988 at the Mount Sinai Medical Center.

Growth of the Pediatric Cardiac Surgical Effort

The past decade and a half has witnessed a sharply increased volume of cardiac operations performed on infants and children. Currently, the department consistently has a pediatric operative volume of four to five open-heart cases each week. In view of the high mortality of many neonates and infants with complex congenital cardiac lesions diagnosed in the first year of life, shortly after Griepp's arrival, the department initiated an open-heart surgical program which specifically focused on this high-risk group. Directed by Griepp, many of the operative procedures were performed on patients who had conditions of deep HCA. Impressive results have been obtained in the correction of defects in deeply cyanotic, high-risk infants with a wide variety of severe lesions, such as pulmonary atresia with ventricular septal defect, various types of transposition of the great arteries and hypoplastic left heart pathology.

Of key importance in the success of this effort was the development of a close-knit CTS-Pediatric Cardiology team. The Pediatric Cardiology group (directed initially by Richard Golinko and later by Ira Parness) was augmented by a number of highly qualified individuals whose experience yielded consistently superb preoperative diagnostic information employing the latest echocardiographic, cardiac hemodynamic and angiographic methods. A pediatric cardiac surgical ICU was staffed on a full-time, twenty-four hour basis by highly experienced pediatric cardiologists, nurses and physician assistants whose specific forte was the management of post-cardiac surgical infants and children. As a key component of the team, over the next few years, Griepp augmented the CTS staff with surgeons of excellent technical competence and specific interest in pediatric cardiac surgery. Ali Sadeghi, a highly qualified surgeon (who had trained under one of this country's finest pediatric cardiac surgeons) was the first to join the Griepp team. In due course, two outstanding young men, both having completed the Mount Sinai CTS residency and subsequently having joined the attending staff, worked closely with Griepp in the cardiac surgical management of the pediatric cases. The first of these colleagues, Cid Quintana, remained on the staff for several years until he was successfully recruited for a leadership position at another institution. Upon his departure, another of Griepp's former CTS residents, Khanh Nguyen (who had spent a fruitful post-residency year as senior registrar on the cardiac surgical service at London's world-renowned Hospital for Sick Children) rejoined Griepp and continues to share responsibility for the pediatric cardiac surgical load.

The collaborative CTS-Pediatric Cardiology team effort has justifiably earned the admiration of other pediatric cardiac surgical programs in the United States and abroad. Indeed, a reflection of the high regard in which the combined team is held has been a number of invitational visits to Russia, Romania and China to perform open-heart procedures on critically ill infants and children.

Coronary Artery Bypass and Valvular Surgery in a Changing Patient Population

In the past decade a broadened spectrum of patients undergoing surgery for either intrinsic coronary artery or valvular heart disease (or both) has become clearly apparent. Patients who in earlier years would never have been considered surgical candidates are now accepted for surgery. Commonly, not only are they older (occasionally in their eighth and ninth decades of life), but they also manifest evidence of diffuse atherosclerotic involvement (coronary, carotid and peripheral arterial obstructive disease, and systemic arterial hypertension which was frequently accompanied by renal dysfunction) and sharply compromised ventricular function, often with coexisting mitral or aortic valvular pathology. Additionally, patients who in earlier years had undergone coronary artery bypass grafting (CABG) primarily with saphenous vein grafts are being accepted for reoperation because of graft occlusion, as are those patients in whom previous direct coronary artery catheter interventions (percutaneous transluminal coronary angioplasty or the more recently introduced atherectomy or stent procedures) have been unsuccessful. Despite frequently severe and multiple preoperative risk factors, the surgical results in these cases are being accomplished with surprisingly low mortality and long-term improvement (42). The higher long-term patency and consistent use of internal mammary arterial bypass grafts more than the less satisfactory saphenous vein grafts is a key component in the impressively effective surgical procedures performed at this institution.

Patients having surgery for either single or multiple valve pathology who are shown to have coexisting coronary artery disease consistently undergo both valvular and CABG surgery. Whenever possible, valvular repair rather than replacement is elected since it offers the major advantage of not requiring the patient to be placed on a permanent anticoagulant regimen, with the attendant drug-related complications.

Cardiopulmonary Transplantation and the Circulatory Support Effort

The institutional decision to establish a multi-organ transplantation program was one of the important factors which attracted Griepp to Mount Sinai. Having been an important participant in the extraordinary cardiac transplantation program at Stanford University, Griepp, upon his arrival at Mount Sinai, immediately established a cardiac transplantation team. He, in collaboration with Valentin Fuster (chief of the Division of Cardiology) and Gail Weissman (vice president, Nursing), quickly organized an effective multi-departmental transplant group. Steven Lansman, who previously had trained under Griepp and who recently had joined the CTS faculty, was selected to direct the program. Assigned to coordinate the myriad medical details so essential to the success of any transplantation effort were Marc Cohen (Division of Cardiology) and Deborah Matza (Department of Nursing). Months of intense planning preceded Mount Sinai's first clinical cardiac transplantation, which was successfully performed on August 28, 1986. Fourteen years later, the patient was in excellent health with no evidence of cardiac rejection. At this writing, Mount Sinai has one of only two approved cardiac transplantation programs in the New York City area.

A major and continuing problem experienced by all transplantation programs has been the relative dearth of suitable donor organs for the many desperately ill patients awaiting lifesaving transplantation. For a rapidly deteriorating cardiac patient whose probable survival could be projected to a period of only days, the deployment of a ventricular assist device (VAD) as a "bridge-to-transplant" has been shown to be a life-saving measure until a suitable donor heart becomes available. Three types of support devices have been employed, but the majority of patients have been supported with the Novacor® device, a superbly designed left ventricular assist device (LVAD), which was first utilized at Mount Sinai in 1996. At this writing, the unit has been employed for periods of up to 272 days in 38 patients awaiting cardiac transplantation. The Novacor® LVAD is sufficiently compact to permit patients to be ambulatory in the hospital, and on occasion, to be discharged from Mount Sinai to their homes while awaiting the news that a suitable donor heart is available.

Pulmonary transplantation became a potential with the recruitment of Ali Sadeghi, an experienced transplant surgeon who joined the CTS faculty in 1990. Sadeghi directed the first combined transplantation effort in which the heart and one lung obtained from a single donor were separately implanted in two critically ill patients. He also performed the first combined heart and lung transplant on a sixteen-year-old patient with advanced congenital cardiopulmonary disease (1992). There also have been three important recent additions to the surgical component of the transplantation group. In April 1999, Paul Waters was appointed professor of CTS, chief of the Division of General Thoracic Surgery and surgical director of the Lung Transplantation Program in the Recanati/Miller Transplantation Institute. Waters is one of the world's most experienced surgeons in lung transplantation. Two other surgeons who had recently joined the CTS faculty were assigned to collaborate with Waters in the lung transplantation effort. Both surgeons had received their CTS tutelage at Mount Sinai under Griepp and both, upon completion of their training, had been accepted for postgraduate study in institutions with world-renowned transplantation reputations. Jock McCullough spent many months working with the highly experienced heart and lung transplantation team at the University of Pittsburgh and David Spielvogel spent a year at the Harefield Hospital (England) working with Sir Magdi Yacoub, the internationally renowned transplant surgeon and unit director.

The passage of time has inevitably been accompanied by a number of personnel changes in the CTS transplant group. In recent years, Alan Gass (division of Cardiology) has assumed directorship of the medical and cardiologic aspects of the transplantation program and collaborates closely with Lansman, his surgical colleagues, and two extraordinary nurses, Mary Courtney, R.N. and Rhodora Correa, R.N. This trio conducts intensive preoperative screening of potential transplantation candidates, carefully follows each patient in the hospital immediately after transplantation, and also maintains careful surveillance of each patient following discharge, with continuing concern for the early detection and management of any evidence of organ rejection.

The fifteen years which have elapsed since Mount Sinai's first cardiac transplantation have witnessed progressive growth of the entire transplantation effort. At this writing, 279 cardiac transplants and 8 combined heart and lung transplants have been performed. The expanding scope of the transplantation program is further reflected by the fact that 15 lung (single and double) transplants have been carried out. Despite the difficult donor organ supply problem, cardiac and pulmonary transplantation at Mount Sinai is a program which justifiably is well respected nationally.

The Research Laboratory (1985 to Present)

Guided by Griepp's continued input over the past decade and a half, day-to-day planning and direction of all laboratory activities was assigned to Ali Sadeghi in the early 1990s, then to Jock McCullough, and, more recently, to David Spielvogel. Over the years, improved understanding and development of possible management approaches to a number of important and unresolved clinical issues have been the central focus of all of the studies. The consistent use of HCA by Griepp and colleagues in the conduct of cardiac and aortic operations, and appreciation that the incidence and severity of neurologic dysfunction correlated directly with the duration of HCA, provided the impetus over the past 15 years for a continuing series of laboratory studies (funded by the NIH). It had two goals: to enlarge our understanding of cerebral pathophysiologic derangements associated with HCA, and to develop management strategies which would utilize methods developed in the experimental laboratory to permit consistently safe use of HCA for 60 minutes or longer.

Utilizing two reliable canine and porcine experimental models developed over a period of years, researchers determined cerebral hemodynamic and metabolic variables and parameters as well as brain stem and spinal cord activity before, during and after HCA. There was excellent correlation between cortical electrophysiologic recovery, clinical behavior of the animals and histopathologic changes (34–37). Thus, the models provided a means of rigorously comparing a variety of management techniques with respect to both physiology and outcome.

A number of important laboratory observations which were made over the years have directly influenced changes in clinical management. The experimental studies demonstrated unequivocally that the protective effect of hypothermia could be enhanced by using more profoundly hypothermic temperatures than those which had been widely employed clinically previously. Of importance was the fact that even under laboratory conditions in which sharply lower blood temperatures were employed, there was evidence that some degree of residual, albeit reduced, cerebral metabolic activity persisted. The implications of the studies were that both the perfusion temperature and the permissibly safe period of HCA had to be lowered, conclusions which have been applied clinically by Griepp and colleagues (43, 44). Currently, investigations are in progress which seek to better understand events and cellular pathologic alterations which are discernible when a cerebral ischemic insult has occurred. The possibility of preventing or mitigating the process of cell damage by utilizing pharmacologic inhibitors of adverse enzymatic activity which play a central role in cell death is under investigation (45–47).

Another important laboratory study sought to understand factors underlying paraplegia, a devastating complication occasionally seen following resection and replacement of segments of the descending thoracic aorta. The clinical procedure requires proximal (upstream) clamping of the aorta for varying periods of time, which necessarily interrupts critical blood flow to the spinal cord, with the resulting potential for paraplegia. An experimental porcine model was developed which precisely simulated varying anatomic and operative conditions encountered when descending thoracic aortic aneurysms and dissections are operated upon (48). The studies revealed that a prolonged period of aortic cross-clamping, with failure to provide blood flow to both intercostal and lumbar arteries (which was shown to be critical to maintenance of spinal cord integrity), is the single most important factor determining the probability of paraplegia. Further, it was determined that it is vital that those arteries providing essential blood flow to the spinal cord be reimplanted into the polyester graft utilized to replace the diseased aortic segment. The results of the experimental study have prompted significant modifications in the operative approach to these cases (49, 50).

The laboratory also studied two specific problems relating to pulmonary transplantation. The possibility that single lung transplantation might be an acceptable therapeutic option for children with specific types of complex congenital heart disease with accompanying poorly developed or absent connections to the lungs prompted an experimental study in which a single lung was successfully transplanted under conditions which simulated that found in severely cyanotic infants and children suffering from the cardiopulmonary lesion described above. The possibility of transplantation of a living related adult donor lobe into a child suffering life-threatening pulmonary disease prompted a second successful laboratory study in which conditions were established in which the animal was entirely dependent on the transplanted lobe or lung. Both types of transplantation studies have the potential for clinical application in the immediate future.

Precise conduct of the research protocols described above required the presence of competent staff with a keen interest in research and the surgical expertise required to establish complex experimental models. A two-year competitive research fellowship was established by Griepp some years ago in which interested surgical investigators were recruited from both the Mount Sinai residency programs (Peter Midulla and Dale Levy) and abroad. Investigators from abroad included Alejandro Gandsas (Argentina), Otto Dapunt and Marek Ehrlich (Austria), Tatu Juvonen (Finland), Christian Hagl (Germany), N. Zhang (People's Republic of China) and M.E. Yerliogl (Turkey). Special mention must be made of a remarkably gifted Mount Sinai School of Medicine student, Craig K. Mezrow, who found himself unexpectedly assuming the role of senior investigator while in the midst of his medical studies. Granted permission for a "sabbatical" absence, which lengthened to a period of five years before he returned to complete his medical studies, young Mezrow played a key role in both the design and conduct of all of the demanding investigations carried out during those years.

The effectiveness and productivity of the laboratory was immeasurably augmented by collaboration with a number of faculty members from other departments: Donald Weisz and Rosario Zapulla (Neurosurgery), David Wolfe (Pathology), Carol A. Bodian (Biomathematics), Nadine A. Tatton (Neurology), and Ian Holzman (Pediatrics).

Conclusion

It has been ninety years since thoracic surgery began at Mount Sinai with Howard Lilienthal's first open chest procedure employing a ventilator designed and constructed by Charles Elsberg. The years that followed have seen incredible advances in both general thoracic and cardiovascular surgery, many of the seminal contributions having been made by Mount Sinai staff members. Notwithstanding all that has been done, the new millennium offers promise that in the fullness of time, all that has been accomplished will pale beside what is yet to be.

So many worlds,
So much to do,
So little done,
Such things to be.
Alfred Lord Tennyson

References

1. Lilienthal H. Thoracic surgery: The surgical treatment of thoracic disease. Vols. I and II. Philadelphia and London: W.B. Saunders; 1926.
2. Ibid (Vol. I), p. 463.
3. Ibid (Vol. I), p. 487.
4. Meltzer SJ, Auer J. Continuous respiration without respiratory movement. J Exp Med 1909; 11:622–625.
5. Lilienthal H. The first case of thoracotomy in a human being under anesthesia by intratracheal insufflation. Ann Surg 1910; 52:30–33.
6. Graham EA. A brief account of the development of thoracic surgery and some of its consequences. Surg Gynecol Obste 1957; 104:241–250.
7. Ottenberg R. Studies in isoagglutination. I. Transfusion and the question of intravascular agglutination. J Exp Med 1911 13:425–438.
8. Lewisohn R. A new and greatly simplified method of blood transfusion: A preliminary report. Med Rec 1915; 87:141–142.

9. Lewisohn R. Blood transfusion by the citrate method. Surg Gynecol Obstet 1915; 21:37–47.
10. Gross RE, Hubbard JP. Surgical ligation of patent ductus arteriosus: A report of first successful case. JAMA 1939; 112:729–731.
11. Graybiel A, Strieder JW, Boyer NH. An attempt to obliterate the patent ductus arteriosus in a patient with subacute bacterial endarteritis. Am Heart J 1938; 15:621–624.
12. Touroff ASW, Vessell H. Experiences in the surgical treatment of subacute streptococcus viridans endarteritis complicating patent ductus arteriosus. J Thorac Surg 1940; 10:59–83.
13. Touroff ASW. The rationale of operative treatment of subacute bacterial endarteritis superimposed on patent ductus arteriosus. Am Heart J 1942; 23:847–856.
14. Blalock A, Taussig HB. The surgical treatment of malformations of the heart. JAMA 1945; 128:189–202.
15. Blumenthal S, Brahms S, Sussman ML. Tricuspid atresia with transposition of the great vessels successfully treated by surgery. J Mt Sinai Hosp 1951; 17:328–335.
16. Berry FB. Preface. In: Surgery in World War II: Thoracic surgery. Vol. II. Office of the Surgeon General. Department of the Army. Washington (DC). 1965. p. xiii.
17. Gadboys HL, Slonim R, Litwak RS. The homologous blood syndrome. I: Preliminary observations on its relationship to clinical cardiopulmonary bypass. Ann Surg 1962; 156:793–804.
18. Litwak RS, Slonim R, Wisoff BG, Gadboys HL. Homologous blood syndrome during extracorporeal circulation in man. II: Phenomena of sequestration and desequestration. N Engl J Med 1963; 268:1377–1382.
19. Jurado RA, Fitzkee HL, deAsla RA, et al. Reduction of unexpected, life-threatening events in postoperative cardiac surgical patients: The role of computerized surveillance. Circulation 1977; 56(3 Suppl):II44–II49.
20. Litwak RS, Gadboys HL, Baron MG, et al. Elective open-heart surgery in mitral stenosis: Experience with pump-oxygenator standby. Am J Cardiol 1965; 16:206–216.
21. Starr A, Edwards ML. Mitral replacement: The shielded ball valve prosthesis. J Thorac Cardiovasc Surg 1961; 42:673–682.
22. Carpentier A, Lemaigre G, Robert L, et al. Biological factors affecting long-term results of valvular heterografts. J Thorac Cardiovasc Surg 1969; 58:467–483.
23. Favaloro RG. Surgical treatment of coronary arteriosclerosis. Baltimore (MD): Williams and Wilkins; 1970.
24. Green GE, Stertzer SH, Gordon RB, Tice DA. Anastomosis of the internal mammary artery to the distal left anterior descending coronary artery. Circulation 1970; 41:II-79–II-84.
25. Jacobson JH, Suarez EL. Microsurgery in anastomoses of small vessels. Surg Forum 1960; 11:243–245.
26. Comroe JH. Retrospectroscope: Insights into medical discovery. Menlo Park (CA): Von Gehr Press; 1977.
27. Estioko MR, Litwak RS, Rand JH. Reoperation, emergency and urgent open cardiac surgery in Jehovah's Witnesses. Chest 1992; 102:50–53.
28. Moulopoulos SD, Topaz S, Kolff WJ. Diastolic balloon pumping (with carbon dioxide) in the aorta: Mechanical assistance to the failing circulation. Am Heart J 1962; 63:669–675.
29. Litwak RS, Koffsky RM, Lukban SB, et al. Implanted heart assist device after intracardiac surgery. N Engl J Med 1974; 291:1341–1343.
30. Cooley DA, Crawford FS, Howell JF, Beall AC, Jr. Open-heart surgery in Jehovah's Witnesses. Am J Cardiol 1964; 13:779–781.
31. Benis AM, Nossel HL, Aledort LM, et al. Extracorporeal model for study of factors affecting thrombus formation. Thromb Diath Haemorrh 1975; 34:127–144.
32. Griepp RB, Stinson EB, Shumway NE. Profound local hypothermia for myocardial protection during open-heart surgery. J Thorac Cardiovasc Surg 1973; 66:731–741.
33. Griepp RB, Stinson EB, Hollingsworth JF, Buehler D. Prosthetic replacement of the aortic arch. J Thorac Cardiovasc Surg 1975; 70:1051–1063.
34. Mezrow CK, Sadeghi AM, Gandsas A, et al. Cerebral blood flow and metabolism in hypothermic circulatory arrest. Ann Thorac Surg 1992; 54:609–616.
35. Mezrow CK, Midulla P, Sadeghi AM, et al. Evaluation of cerebral metabolism and quantitative electroencephalography after hypothermic circulatory arrest and low-flow cardiopulmonary bypass at different temperatures. J Thorac Cardiovasc Surg 1994; 107:1006–1019.
36. Mezrow CK, Gandsas A, Sadeghi AM, et al. Metabolic correlates of neurologic and behavioral injury after prolonged hypothermic circulatory arrest. J Thorac Cardiovasc Surg 1995; 109:959–975.
37. Mezrow CK, Midulla PS, Sadeghi AM, et al. Quantitative electroencephalography: A method to assess cerebral injury after hypothermic circulatory arrest. J Thorac Cardiovasc Surg 1995; 109:925–934.
38. Dapunt OE, Galla JD, Sadeghi AM, et al. The natural history of thoracic aneurysms. J Thorac Cardiovasc Surg 1994; 107:1323–1333.
39. Juvonen T, Ergin MA, Galla JD, et al. Prospective study of the natural history of thoracic aortic aneurysms (J. Maxwell Chamberlain Memorial Paper). Ann Thorac Surg 1997; 63:1533–1545.
40. Juvonen T, Ergin MA, Galla JD, et al. Risk factors for rupture of chronic type B dissections. J Thorac Cardiovasc Surg 1999; 117:776–786.
41. Griepp RB, Ergin MA, Galla JD, et al. Natural history of descending thoracic and thoracoabdominal aneurysms. Ann Thorac Surg 1999; 67:1927–1930.
42. Lansman SL, Cohen M, Galla JD, et al. Coronary bypass with ejection fraction of 0.20 or less using centigrade cardioplegia: Long term follow-up. Ann Thorac Surg 1993; 56:480–486.
43. McCullough JN, Zhang N, Reich D, et al. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg 1999; 67:1895–1899.
44. Hagl C, Ergin MA, Galla JD, et al. Neurological outcome after ascending aorta-aortic arch surgery: Impact of brain protection techniques in high risk patients. J Thorac Cardiovasc Surg 2001; 121:1107–1121.
45. Hagl C, Tatton NA, Weisz DJ, et al. Cyclosporine A as a potential neuroprotective agent: A study of prolonged hypothermic circulatory arrest in a chronic porcine model. Eur J Cardiothorac Surg 2001; 19:756–764.
46. Hagl C, Tatton NA, Khaladj N, et al. Involvement of apoptosis in neurological injury following hypothermic circulatory arrest: A new target for therapeutic interventions? Ann Thorac Surg 2001; 72:1457–1464.
47. Tatton NA, Hagl C, Nandor S, et al. Apoptotic cell death in the hippocampus due to prolonged hypothermic circulatory arrest: Comparison of cyclosporine A and cycloheximide on neuron survival. Eur J Cardiothoracic Surg 2001; 19:746–755.
48. Dapunt O, Midulla PS, Sadeghi AM, et al. Pathogenesis of spinal cord injury during simulated aneurysm repair in a chronic animal model. Ann Thorac Surg 1994; 58:689–697.
49. Griepp RB, Ergin MA, Galla JD, et al. Looking for the artery of Adamkiewicz: A quest to minimize paraplegia after operations for aneurysms of the descending thoracic and thoracoabdominal aorta. J Thorac Cardiovasc Surg 1996; 112:1202–1215.
50. Griepp RB, Ergin MA, Galla JD, et al. Minimizing spinal cord injury during repair of descending thoracic and thoracoabdominal aneurysms: The Mount Sinai approach. Semin Thorac Cardiovasc Surg 1998; 10:25–28.

The History of Thoracic Surgery at Mount Sinai

Paul A. Kirschner, M.D.

Abstract

The birth, development and maturation of thoracic surgery at The Mount Sinai Hospital, and its pioneering contributions are presented.

These achievements were accomplished not only by the individual surgeons who had an abiding interest in the surgery of the chest, but also with the fruitful collaboration of pathologists, radiologists, cardiologists, pulmonologists, endoscopists, neurologists, immunologists, and others. Continuing interactions of these specialists promise to yield new and important advances in the field of thoracic surgery at Mount Sinai.

Key Words: Thoracic surgery, The Mount Sinai Hospital, history of thoracic surgery.

The seeds of thoracic surgery at The Mount Sinai Hospital were planted in 1880, when 32-year-old Dr. Arpad C.G. Gerster, a Hungarian émigré, was appointed to the attending staff as visiting surgeon. Seven years later, in 1887, these seeds began to germinate when Dr. Howard Lilienthal, native-born American and Harvard graduate, was appointed house surgeon, having stood first in the competitive examination for internship.

Different as these two were in family and national origins, education, medical training and extracurricular talents, they combined to form a dynamic partnership to establish thoracic surgery as a specialty at Mount Sinai.

Gerster's autobiography, *Recollections of a New York Surgeon* (1), is a remarkable account of his personal and professional life, precise in detail and crystal clear in syntax and grammatical expression. He was born in 1848 in Kassa in the Austro-Hungarian Empire (today Kosice, Slovakia). He was a Hungarian Catholic, although apparently not strictly observant, tracing his family back to the 16th century in Switzerland. After a classical early education in the *Gymnasium* tradition, he attended the University of Vienna, earning, *en passant,* a sabre-cut in a tendon of his little finger in a ceremonial duel. He earned his medical degree in Vienna under Billroth, Rokitansky and Skoda.

In 1874 he emigrated to the U.S., settling in Brooklyn, but on the way to the boat he visited Volkmann's clinic in Halle, Germany, where he observed the new Listerian method of antiseptic surgery using carbolic acid spray. This must have made an enormous impression on him, as he was to write, some 14 years later in 1888, a landmark American book, *The Rules of Aseptic and Antiseptic Surgery*, which ultimately went through three editions (2).

The primitive state of thoracic surgery in those early days is best illustrated by the case history of one Louis Stix, a Mount Sinai trustee whom Gerster was called to see in consultation in 1882. The patient presented with chills and fever, a draining, purulent sinus alongside the sternum, an irregular pulse, and cardiac displacement by a mediastinal mass. Successful curative surgery was carried out, consisting of debridement and resection of osteomyelitis of the sternum, along with drainage of a mediastinal abscess caused by *Mycobacterium tuberculosis*, which had been identified by Koch in that year. This was before X-rays (discovered in 1895), electrocardiogram (1903), and intratra-

---

Professor Emeritus of Cardiothoracic Surgery, Mount Sinai School of Medicine, New York, NY.

Address correspondence to Paul A. Kirschner, M.D., 331 College Road, Bronx, NY 10471.

Accepted for publication March 2003.

cheal anesthesia (1910), and without intensive care units, blood transfusion, etc. In gratitude, Mr. Stix exercised his influence in facilitating Gerster's election to the prestigious New York Surgical Society.

In 1887, a future giant in the new specialty of thoracic surgery stood first in the competitive examination for internship at Mount Sinai. His name was Howard Lilienthal. Born in Albany, NY in 1861, he was the oldest child of immigrant parents from Germany. He attended the Albany Boys Academy and graduated from Saratoga High School in 1877. After two years of private tutoring he matriculated at Harvard College, graduating cum laude in 1883. At Harvard, his extracurricular interests included choral singing (he sang at Henry Wadsworth Longfellow's funeral) and wrestling (he was small, but wiry). Upon graduation, he entered Harvard Medical School, earning his medical degree in 1887, at which time he took the Mount Sinai internship examination. He archly tells of himself that, having ranked first in the examination, he committed a "social error" by choosing the surgical rotation to house surgeon over the traditional first choice of the medical rotation. He states that he did not love medicine less, but that he loved surgery more. Years later, another Mount Sinai great, George Baehr, future attending physician, also chose the surgical over the medical internship, because he wanted to study under Gerster (Lilienthal's mentor). Baehr later became the first full-time chief of the medical service in 1945.

After completing his internship, Lilienthal went into practice and became Gerster's assistant. In 1890 he was appointed assistant attending surgeon and in 1899 was elevated to the rank of full attending. The Surgical Department was then divided into two services, one led by Gerster and one by Lilienthal. Lilienthal began to develop his thoracic surgical expertise in cases of pleural and pulmonary suppuration, an expertise which led ultimately to pioneering accomplishments in pulmonary resection (lobectomy) (3) and other aspects of thoracic surgery.

One of the younger attending surgeons on Lilienthal's service was Charles Elsberg, who had, in the early 1900s, conducted animal research on "intratracheal insufflation" anesthesia at the Rockefeller Institute, under Samuel Meltzer and John Auer, both internists. The first-ever clinical application of this technique for thoracotomy in a human being was carried out at Mount Sinai in 1910 by Lilienthal, with Elsberg administering the anesthesia (4, 5). Endotracheal anesthesia, as it is now called, has become an essential part of thoracic surgery.

One collateral benefit of this experience with "intratracheal insufflation" (5) was its application in a female patient with severe myasthenia gravis in crisis, in acute respiratory failure. She was kept alive by this method for several hours. This technique of artificial ventilation for the treatment of the various types of respiratory failure, with subsequent modern embellishments, is routinely used today in critical care units all over the world.

In 1914, coincident with the retirement of Arpad Gerster, the entire Surgical Department was completely reorganized. Four services were created, each with a major specialty over and above the "routine" general surgery of the day. These were (a) Thoracic Surgery, under Howard Lilienthal, (b) Neurosurgery, led by Charles Elsberg, now specializing in this field, (c) Surgery of the Stomach and Duodenum, under A.A. Berg, also a former assistant of Gerster, who became famous for skill in surgery for peptic ulcer, and (d) Kidney, Ureter and Bladder, under Edwin Beer, pioneer in the endoscopic treatment of bladder tumors. This reorganization persisted up until the mid-1940s, after which the full-time system was inaugurated.

Each of these four surgical services became the nucleus of multidisciplinary specialty groups. The members of the thoracic disease group included Harry Wessler and Coleman B "Kelly" Rabin in pulmonology, radiology and pathology, Sidney Yankauer, Rudolf Kramer and Max Som in bronchoscopy, and others to be mentioned later. This group, in somewhat altered form, content and scope, continues to function today as the Department of Pulmonary and Critical Care Medicine.

Shortly after this reorganization took place, World War I began, and the hospital became involved in the war effort. U.S. Base Hospital No. 3 was constituted, with Major, later Lt. Col. Howard Lilienthal as its chief medical officer. Lilienthal was eager to be involved in the surgery of the severely wounded and for a time was on detached service with advanced surgical teams assigned to Evacuation Hospital No. 8 and U.S. Army Hospital No 101. Tragically, his son, an infantry officer, was killed in action just a few weeks before the Armistice.

On his return from overseas, Lilienthal resumed his hospital activities, adding to his large series of lobectomies for suppurative lung disease (3), developing the technique of esophagectomy for cancer of the esophagus (6), promoting early diagnosis and treatment of lung cancer (7) and fostering the recognition of thoracic surgery as a specialty (8).

Lilienthal was also active in the thoracic surgical community. In 1917, he, with Willy Meyer of Lenox Hill Hospital and a few others, founded the New York Society for Thoracic Surgery, now the oldest thoracic surgical society in the world. With this society as a base, the American Association for Thoracic Surgery was founded later that year. Today it is recognized as the premier thoracic surgery organization in the world.

Down through the years, Mount Sinai thoracic surgeons have continued to be active in the New York Society for Thoracic Surgery. Among those serving as president included Paul A. Kirschner, Robert S. Litwak, Randall B. Griepp, M. Arisan Ergin and Steven Lansman.

Other founding members of the New York and the national societies, from Mount Sinai, included Martin Ware, Sidney Yankauer (bronchoscopist), Abraham Wilensky, William Branower (anesthetist), Morris Manges (internist) and Charles Elsberg. Lilienthal became the president of the national society in 1922. His presidential address (7) was entitled "Malignant Tumor of the Lung: Necessity for Early Operation." In it, for the first time, he made a clear distinction between the two main topographical types of lung cancer: the central large bronchus type and the peripheral parenchymal type. This represented the beginning of the staging system so widely used today. In 1925, he clearly outlined the rationale for "thoracic surgery as a specialty" (8), antedating the specialty boards by more than 20 years.

When Lilienthal retired from active ward service in 1923, the Medical Board honored him by assigning six "ward" beds for his personal patients for the following year, so that he could continue his pioneering work (9). He published a two-volume text book on thoracic surgery (10) in 1926, the first such publication of its kind in the United States, and between his "retirement" from ward service in 1923 and his death in 1946, he authored more than 60 additional publications, remaining a never-ending source of knowledge in thoracic surgery.

Between 1923 and 1934, the Thoracic Surgery Service was led by Alexis V. ("AV") Moschcowitz and then Richard Lewisohn. "AV" was the older brother of Eli Moschcowitz (a future chief of the medical service) and was noted mainly for his contributions to hernia surgery and for devising a successful operation for prolapse of the rectum. Less well known are Dr. Moschcowitz's important contributions to thoracic surgery, including a classic text on the treatment of diseases of the costal cartilages (11) and his service on the Empyema Commission of the U.S. Army during the First World War. Other commission members included Major Evarts Graham (from Washington University Medical School, St. Louis), the chairman, and Lt. Frederick Zeman from Mount Sinai. The commission was seeking a reason for the very high postoperative mortality rate for empyema in the U.S. Army. At that time, the world-wide epidemic of influenza (sometimes called the "Spanish flu") was raging, and contagion was rife in the crowded barracks of the Army training camps. Empyema was a very common complication of the post-influenza pneumonia. Standard treatment of empyema then was wide-open thoracostomy drainage. This was attended by a frightful mortality rate, at times exceeding 50%. The commission determined that the cause of death in most instances was not the empyema per se, but "anoxemia" secondary to the collapsed lung which was also the seat of pneumonia. By changing from "open" to "closed" drainage of the empyema using a chest tube, thus maintaining lung expansion and pulmonary function, the surgeons were able to lower the mortality rate to low single-digit numbers (12). Evarts Graham, a noted pioneer in thoracic surgery, who later performed the first successful total pneumonectomy for lung cancer (in 1933), was awarded the prestigious Samuel Gross Prize in Surgery in 1925 for his report of the work done by the Empyema Commission. Later, as an attendant physician at Mount Sinai, Dr. Zeman became one of the founders of the specialty of geriatrics.

Richard Lewisohn, who followed Dr. A.V. Moschcowitz on the Thoracic Surgery Service, was primarily a gastric surgeon. He is best known for developing "citrated" blood transfusion, which led to blood banking (13). This process became a cornerstone in the development and growth of modern thoracic surgery (14).

During the period 1923–1930, the bulk of thoracic surgery was done by associate surgeon Dr. Harold Neuhof, who rose to the rank of attending surgeon in charge of Thoracic Surgery in 1930. He was born in New York City in 1884 and raised and educated there, earning his medical degree at the College of Physicians and Surgeons of Columbia University in 1905. He graduated from his Mount Sinai internship as house surgeon in 1907 and spent the next year as resident in the private pavilion under Gerster and Lilienthal.

He always exhibited a wide range of medical-surgical interests, especially in confronting the challenges of severely life-threatening diseases. Thus, he displayed an early interest in transplantation, authoring in 1923 "The Transplantation of Tissues" (15). He did a xenograft of a lamb's kidney to a young woman with acute renal failure due to bichloride of mercury poisoning. Needless to say, the graft failed in a few days. But this attempt to expand the frontier of medical sciences was characteristic of Dr. Neuhof.

He went on to confront other diseases, such as venous thrombosis and pulmonary embolism (16), mediastinitis (17) and lung cancer (18–20). In 1932, he and Harry Wessler (see below) published a paper in the *Journal of Thoracic Surgery* (21) entitled "Putrid Lung Abscess — Its Etiology, Pathology, Clinical Manifestations, Diagnosis and Treatment." It served as an inspiration and template for the study of this disease; at least 26 papers on aspects of this subject appeared within the next 15 years. In 1987, more than 50 years later, Earle W. Wilkins, Jr., of Harvard acknowledged the validity and importance of this contribution in his article "Classics in Thoracic Surgery" (22).

Mount Sinai's first thoracic disease group, as indicated above, consisted of non-surgeons representing the many specialties essential to the integrated treatment of thoracic surgical patients. The first of these pioneers was Dr. Harry Wessler, internist and radiologist, who clarified the difference between aspiration lung abscess and other forms of suppurative pulmonary disease (23). This led to the understanding of "putrid lung abscess" and to its successful surgical treatment.

Wessler was the mentor of Dr. Coleman B. ("Kelly") Rabin, who was active from the 1930s to the 1970s and beyond. Like Wessler, Rabin was also an internist, radiologist and pathologist. His contributions included research on the pathology of mesothelioma and studies on so-called "bronchial adenoma" (now known as carcinoid tumor). He devised a method for the precise localization of lung abscess, which was necessary for successful surgery of that condition. He collaborated with Neuhof, Arthur H. Aufses, Sr., and Irving Sarot on a proposed topographic classification of lung cancer, a forerunner of the modern staging system. And he co-authored a textbook on radiology of the chest with Dr. Murray Baron (24), much as Wessler had done with Leopold Jaches (25), then radiologist to the hospital, in earlier years.

Together with Neuhof, Rabin persuaded Dr. Ameil Glass, house staff graduate and fellow, and Dr. Rudolph Kramer, bronchoscopist, to study the anatomical basis for bronchoscopic drainage of lung abscess. From this investigation, based on lung dissections, the concept of the "bronchopulmonary segment" developed (26). Recognized today as a momentous advance in the surgical anatomy of the lung, this laid the groundwork for the localization and precise drainage of lung abscess, and the anatomical basis for precise pulmonary resection.

Other members of the thoracic disease group included Dr. Herman Hennell, internist and TB specialist, Sylvan Moolten, pathologist, Leo Stern, dentist, Daniel Stats, hematologist, Irving Selikoff, noted for his work on tuberculosis and asbestos, Herman Schwartz, pediatrician, and Louis Siltzbach, sarcoidosis specialist, among others. In 1974, Dr. Alvin Teirstein was appointed Chief of the Division of Pulmonary and Critical Care Medicine.

The thoracic surgeons on the service after Neuhof included Arthur S.W. Touroff, associate surgeon and main collaborator with Neuhof on lung abscess, Arthur H. Aufses, Sr., who did research on topographic classifications of lung cancer, Irving Sarot, who studied pulmonary resection, including pleuropneumonectomy in tuberculosis, and Gabriel P. Seley, who specialized in lung cancer and lung abscess.

After Neuhof's retirement in 1946, Arthur Touroff became the new director of the Thoracic Surgical Services. Touroff pioneered the nascent field of cardiac surgery with work on such subjects as "blue babies" and infected patent ductus arteriosus.

The massive socioeconomic upheaval caused by World War II, coupled with spectacular advances in scientific medicine, would completely change the nature of medical practice, hospital organization and patient care. Thoracic surgery was in the forefront of these changes.

First, the widespread adoption of medical and hospital insurance led to hospital reorganization on many levels. The traditional separation of "ward" (charity) patients and "private" (paying) patients was rapidly obliterated and the separate house staffs were now merged. This was accompanied by the appointment of a full-time professional staff in charge of all patients — ward and private.

The first such full-time directors were in the Department of Medicine: Drs. George Baehr and Isidor Snapper. In 1952, Dr. Mark Ravitch followed Dr. Touroff as full-time director of the entire Surgical Service. Trained in The Johns Hopkins tradition (Halsted and Blalock) and imbued with the concept that a "general" surgeon should have expertise in all subdivisions of surgical specialties, Ravitch remodeled and amalgamated the Department of Surgery into a more amorphous entity. Thoracic Surgery as an identifiable separate service entity gave way to *ad hoc* assignments of "qualified" thoracic surgeons for the care of thoracic surgical patients. However, it should be noted that it was only just a few years before, in 1948, that the Board of Thoracic Surgery was created as a subsidiary of the American Board of Surgery, thus validating Lilienthal's plea in 1925 for the recognition of thoracic surgery as a specialty (8). Ultimately, in 1971, a free-standing American Board of Thoracic Surgery was established.

Ravitch's tenure as full-time director antagonized some of the voluntary attending surgeons, leading to his early resignation in 1955. This had all the earmarks of a "town vs. gown" situation.

The type of thoracic surgery practiced at this time now began to undergo a qualitative change. Pulmonary infections (abscess and bronchiectasis) and tuberculosis were coming under control by means of antibiotics, decreasing the need for operative intervention. Cardiovascular surgery, initially of the "closed" heart type, began to emerge as a new specialty. Because of its steeply rising incidence, lung cancer was rapidly becoming a major surgical problem.

Between 1955 and 1957, Dr. John Garlock, attending surgeon to the hospital, served as interim director. While he was best known as a master abdominal and alimentary tract surgeon, he had distinguished himself as a world pioneer in surgery of the esophagus (27), dating back to his earliest contributions in the 1940s. Garlock was a founding member of the boards of Thoracic Surgery, General Surgery, and Plastic Surgery.

In 1957, the second full-time Director of Surgery, Dr. Ivan D. Baronofsky, was appointed. The turmoil that had occurred with Dr. Ravitch's tenure recurred and culminated in Baronofsky's resignation in 1959. Cardiac surgery, essentially "closed heart" surgery for congenital and acquired heart disease, was now becoming technically feasible. By 1960, the development of pump-oxygenators and cardiopulmonary bypass would open the door to the explosive growth of "open heart" surgery as we know it today. During his tenure at Mount Sinai, Baronofsky instituted and developed a successful open-heart surgery program, which has persisted to this day.

During the tenures of Ravitch and Baronofsky (through 1960), the general thoracic surgery service functioned much as a "government in exile," as if it had no official identification. However, over the next forty plus years, it developed into a specifically designated service.

After an interim stewardship from 1959–1960 under Dr. Samuel H. Klein, Dr. Allan E. Kark was appointed full-time director of the Department of Surgery in 1962. Dr. Kark was a native of South Africa who trained at a number of hospitals in England and served as a Fellow in Surgery at the University of Chicago. He later chaired the Department of Surgery at the University of Witwatersrand in Durban, South Africa. One of Dr. Kark's first official acts in 1962 was to recruit Dr. Robert S. Litwak of Miami University to head a newly formed Division of Cardiothoracic Surgery. Dr. Litwak was actually a second-generation cardiothoracic surgeon, having trained under the famed pioneer in cardiac surgery, Dr. Charles P. Bailey.

Dr. Litwak was accompanied by his able associate and collaborator, Dr. Howard Gadboys, to direct the experimental laboratory. The rest of the attending staff, all still voluntary, comprised those surgeons, mainly Drs. Paul A. Kirschner, Bernard P. Robinson, Fouad Lajam, Daniel J. Krellenstein, and Steven Herman, who dealt with problems of the lung, pleura, mediastinum and esophagus — coming to be known as "general thoracic surgery." This latter group, combined with the full-time cardiac surgeons, constituted a well-balanced staff for patient care, teaching and research.

Drs. Kark and Litwak also established a two-year residency training program which met the requirements of the Board of Thoracic Surgery. The board itself, which had been established in 1948, became in 1971 the free-standing American Board of Thoracic Surgery, further validating Howard Lilienthal's dream of "thoracic surgery as a specialty." In 1983 the two-year residency training program was expanded to three years to handle the ever-increasing complexity and volume of surgery of the chest and heart. This was one of the first three-year programs in the country.

Upon his arrival at Mount Sinai, Dr. Litwak established a series of "Lilienthal lectures" in honor of the field's great pioneer. This lecture series ran for more than 10 years, attracting famous speakers from around the world.

For the next twenty or more years the "general thoracic surgeons" dealt with a growing number of problem cases of lung cancer, pleural tumors and infections and, especially, mediastinal disease. Following the description of mediastinoscopy in 1959 by Eric Carlens of Sweden and its introduction to North America by F. Griffith Pearson in 1965, this procedure was adopted for cases of lung cancer and mediastinal tumors. Fifty such patients were operated on at Mount Sinai and reported in 1967 (28). Mediastinoscopy soon became a routine staging procedure for lung cancer and remains to this day one of the foundations of the staging system.

A landmark advance stemming from the experience with mediastinoscopy was its application to thymectomy for myasthenia gravis (see below). Mount Sinai had been a leader in the study and treatment of myasthenia gravis under the direction of Dr. Kermit Osserman from 1951 until his death in 1972. In 1952, Osserman described the use of the "Tensilon" test (29), and his clinical classification of myasthenia gravis is still in use today (30).

Mount Sinai now had the one of the two largest myasthenia gravis clinics in the world (along with The Massachusetts General Hospital). The procedure of thymectomy, stimulated by the work of Blalock, Keynes and Clagett, was carried out via a major chest or sternal-splitting incision to handle both thymomatous and non-thymomatous myasthenia gravis.

Our previous experience at Mount Sinai with mediastinoscopy helped us "rediscover" and embellish the long-forgotten technique of "transcervical" thymectomy, which had been done at the beginning of the 20th century in infants and children for respiratory distress attributed (incorrectly) to so-called "status thymicolymphaticus."

In 1967, the first of a series of 21 cases of transcervical thymectomy was done at Mount Sinai; the series was reported in JAMA in 1969 (31), by Kirschner, Kark and Osserman. This technique was soon adopted worldwide, but not without reservation or even vehement objections by some surgeons. The issue is still being debated today. Mount Sinai became a referral center for thymectomy. In this current era of minimally invasive surgery, transcervical thymectomy is probably the first of such minimally invasive techniques. By 1989, Dr. Angelos Papatestas had performed almost 1,000 such operations. Unfortunately, his untimely death that year cut short a brilliant career.

Over the past 50 years, thymomas and other mediastinal tumors such as teratomas, germ cell tumors and neurogenic tumors have also become commonplace on the General Thoracic Surgery Service.

Dr. Kark resigned in 1974 and was immediately replaced by a Mount Sinai surgeon "born and bred" — Dr. Arthur H. Aufses, Jr. Dr. Aufses came from a Mount Sinai thoracic surgical family. His father, Arthur H. Aufses, Sr., had served as attending surgeon. His mother, Beatrice, served as a volunteer to the Surgical Service under Dr. Harold Neuhof. Arthur Jr., who had been Dr. Ravitch's chief resident, left Mount Sinai to serve as chairman of surgery at Long Island Jewish Hospital. He returned to Mount Sinai as professor and chairman of Surgery following Dr. Kark's departure. He was always supportive of the Cardiothoracic Surgery Service.

In 1979, Dr. Paul A. Kirschner was designated chief of the General Thoracic Surgery Section of Cardiothoracic Service. Kirschner made the transition from voluntary attending to full- time attending in 1991 and served until 1998.

In 1985, Dr. Randall B. Griepp succeeded Dr. Robert S. Litwak as chief of the Division of Cardiothoracic Surgery, inheriting a superb legacy from Dr. Litwak.

In 1990, the Division of Cardiothoracic Surgery became a free-standing department, with Dr. Griepp as chairman. Dr. Griepp's area of expertise included the field of cardiac and pulmonary transplantation, of which he was a pioneer. Under Dr. Griepp, his then-associate Dr. Ali Sadeghi performed lung transplants with a high degree of success. This program was temporarily discontinued when Dr. Sadeghi departed.

In 1998, Dr. Kirschner stepped down and was replaced by Dr. Stephen Keller, who served a brief 18 months.

In 1999, Dr. Paul Waters was appointed chief of General Thoracic Surgery. Waters was especially concerned with lung transplantation, having had a large experience in Toronto and southern California.

Again there was a regime change when Dr. Griepp stepped down in 2001 and was succeeded by Dr. David Adams of Boston as chairman of the Cardiothoracic Surgery Department. Dr. Scott Swanson, also of Boston, became chief of the General Thoracic Surgical Division. Dr. Swanson is now leading a vigorous and growing program in general thoracic surgery, including esophageal surgery and minimally invasive techniques in pulmonary resection.

The writer of this report has been honored to be a part of the great traditions of healing, research, and innovation in the specialty of general thoracic surgery at Mount Sinai.

References

1. Gerster A. Recollections of a New York surgeon. New York: Paul B. Hoeber; 1917.
2. Gerster A. The rules of aseptic and antiseptic surgery. New York, London: Appleton and Company; 1888.
3. Lilienthal H. Resection of the lung for suppurative infections with a report based on 31 operative cases in which resection was done or intended. Ann Surg 1922; 75:259–310.
4. Lilienthal H. The first case of thoracotomy in a human being under anesthesia by intratracheal insufflation. Ann Surg 1910; 52:30–33.
5. Elsberg C. Clinical experience with intratracheal insufflation (Meltzer) with remarks upon the valve of the method for thoracic surgery. Ann Surg 1910; 52:23–29.
6. Lilienthal H. Carcinoma of the thoracic esophagus. Successful resection. Ann Surg 1921; 74:116–117.
7. Lilienthal H. Malignant tumor of the lung: necessity for early operation. Arch Surg 1924; 8:308–316.
8. Lilienthal H. Thoracic surgery as a specialty. Ann Surg 1925; 81:1191–1197.
9. Annual Report of The Mount Sinai Hospital President. 1922:23.
10. Lilienthal H. Thoracic surgery. Philadelphia: W.B. Saunders; 1926.
11. Moschcowitz AV. The treatment of diseases of the costal cartilages. Ann Surg 1918; 68:168–182.
12. Dunham EK, Graham EA. Cases of empyema at Camp Lee, VA and preliminary report by the Empyema Commission, Camp Lee, Petersburg, VA. JAMA 1918; 71(5):366–373 and JAMA 1918; 71(6):443–448.
13. Lewisohn R. The new and greatly simplified method of blood transfusion. A preliminary report. Med Record (NY) 1915; 87:141–142.
14. Lewisohn R. The development of the technique of blood transfusion since 1907. J Mt Sinai Hospital 1944; 10:605–622.
15. Neuhof H, Hirshfeld S. The transplantation of tissues. New York, London: D. Appleton & Co., 1923.
16. Neuhof H. Venous thrombosis and pulmonary embolism. New York: Grune and Stratton; 1948.
17. Neuhof H, Jemerin EE. Acute infections of the mediastinum. Baltimore: Williams and Wilkins; 1943.
18. Rabin CB, Neuhof H. A topographic classification of primary cancer of the lung: its application to the operative indications and treatment. J Thorac Surg 1934; 4:147 ff.
19. Neuhof H, Rabin CB, Sarot IH. Topographic classification of cancer of the lung with special reference to the surgical implications of the circumscribed variety. J Thorac Surg 1942; 11:388–395.
20. Neuhof H, Aufses AH. Cancer of the lung. Interval and late results of operation in relation to topography and gross pathology. J Thorac Surg 1948; 17:297–305.
21. Neuhof H, Wessler H. Putrid lung abscess — its etiology, pathology, clinical manifestations, diagnosis and treatment. J Thorac Surg 1931–1932; 1:637–649.
22. Wilkins EW, Jr. Classics in thoracic surgery. Acute putrid abscess of the lung. Ann Thor Surg 1987; 44:560–559.
23. Wessler H. Suppuration and gangrene of the lung. JAMA 1919; 73:1918–1921.
24. Rabin CB, Baron MG. Radiology of the chest. Baltimore (MD): Williams and Wilkins; 1980.
25. Wessler H, Jaches L. Clinical roentgenology of diseases of the chest. Troy (NY): Southworth; 1923.
26. Glass A. The bronchopulmonary segment with special reference to putrid lung abscess. Am J Roentgenol 1934; 31:328–332.
27. Garlock JH, Klein SH. Surgical treatment of carcinoma of the esophagus and cardia. Analysis of 457 cases. Ann Surg 1954; 139:1–34.
28. Kirschner PA. Mediastinoscopy. Experience with fifty cases. J Mt Sinai Hosp 1967; 34:559–573.
29. Osserman KE, Kaplan LE. Rapid diagnostic test for myasthenia gravis. Increased muscle strength without fasciculation, after administration of edrophonium bromide (Tensilon) chloride. JAMA 1952; 150:265–268.
30. Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med 1971; 38:497–537.
31. Kirschner PA, Osserman KE, Kark AE. Studies in myasthenia gravis. Transcervical total thymectomy. JAMA 1969; 209:906–910.

Minimally Invasive Endocrine Surgery

MICHAEL D. ADDIS, M.D., AND WILLIAM B. INABNET, M.D.

Abstract

Background: Minimally invasive endocrine surgery has experienced multiple new developments.
Methods: Comprehensive review of the literature.
Conclusions: Minimally invasive techniques can be efficaciously and safely applied to most endocrine disorders. Endocrine surgeons should be skilled in these techniques in order to individualize the operative approach.

Key Words: Laparoscopy, parathyroidectomy, adrenalectomy, thyroidectomy, minimally invasive endoscopy.

Introduction

LAPAROSCOPY has revolutionized surgery over the past decade. As with so many other diseases and conditions heretofore requiring general surgery, the advances made in minimally invasive technique have changed the treatment of endocrine disease. In fact, endoscopic surgery has become the preferred approach for many of the benign endocrine diseases. Various approaches have been described in the literature for the same diseases; hence, much debate exists over which methods are most efficacious. This article will review the approaches currently being discussed, in an attempt to highlight the indications and advantages/disadvantages of each method.

Laparoscopic Adrenalectomy

Laparoscopic adrenalectomy, first described by Gagner and colleagues in 1992, has become the procedure of choice for the removal of most adrenal pathology (1). Although a technically challenging procedure, surgeons with advanced laparoscopic technique can learn how to perform this operation in a safe, efficient manner.

The meticulous preoperative work-up of patients with adrenal disease must encompass both chemical and radiographic studies to diagnose and localize pathology. In particular, it is important to investigate the possibility of multiple endocrine neoplasia (MEN) syndromes, particularly in a patient with a diagnosed pheochromocytoma and a significant family history. When investigating a particular lesion, 24-hour urinary catecholamines and metabolites, cortisol, aldosterone and testosterone/estrogen levels are measured to help determine the cellular origin. In addition, computed tomography (CT) scans, magnetic resonance imaging (MRI), and scintigraphy (i.e., meta-iodobenzyl guanidine I 123 [MIBG] scan for pheochromocytoma) are important radiographic modalities to use in its identification and localization (2). It is generally agreed that all functioning adrenal tumors should be resected, regardless of size. For incidentally detected, nonfunctioning tumors, the size of the lesion plays a role in recommending surgery. Lesions smaller than 3 cm can be followed with close surveillance, whereas lesions larger than 6 cm should be resected, due to the increased risk of malignancy. Nonfunctioning adrenal masses of an intermediate size (i.e., 3–6 cm) should be approached on a case-by-case basis: younger

---

From the Division of Laparoscopic Surgery, Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to William B. Inabnet, M.D., Box 1259, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; email: b.inabnet@mountsinai.org

Updated as of May 2003.

patients may benefit from adrenalectomy, whereas surveillance may be preferred for older patients.

Although there are some relative and absolute contraindications to laparoscopy, the vast majority of patients would benefit from this approach. Various studies have investigated the advantages and disadvantages of laparoscopic vs. open adrenalectomy. Prinz compared these two approaches directly for patients with unilateral lesions less than 10 cm in diameter (3). The two open procedures included in the study were the transabdominal and posterior approaches. The length of the procedure was not significantly different, particularly as experience in the laparoscopic approach improved. More significant, however, were the shorter length of stay and decreased use of postoperative analgesics. Gagner et al. (5) had similar results when they studied 100 consecutive laparoscopic adrenalectomies. In addition, they considered the absolute and relative contraindications to the procedure. Essentially, the only absolute contraindication is a patient with adrenal carcinoma. The possibility of local disease requiring extensive *en bloc* resection makes the open technique a more favorable choice. Relative contraindications include patients with lesions larger than 10 cm, a history of multiple intra-abdominal operations, and diagnosis of malignant pheochromocytomas that extend into periaortic lymph nodes (4, 5). MIBG scans or MRI may localize these malignant lesions and thus influence the decision to perform an open procedure (4). In addition, large lesions with an extensive vascular supply would allow only limited exposure for dissection; thus, an open approach may be safer and potentially less time-consuming (5).

The laparoscopic retroperitoneal approach has also been described in the literature. Unlike the transabdominal techniques described by Gagner and Prinz, the retroperitoneal approach does not provide the ability to explore the abdomen for malignancy and can limit the visibility needed for dissection. On the other hand, a retroperitoneal dissection may be advantageous for patients with a history of prior abdominal surgery and for those requiring bilateral adrenalectomy. Although most surgeons utilize the transabdominal approach, the retroperitoneal technique is a viable option (2).

Laparoscopic resection of pheochromocytomas has been a subject of debate since the approach was first described. Some surgeons argue that intraoperative cardiovascular stability would be at greater risk with laparoscopy because of CO_2 pneumoperitoneum. Various studies have concluded, however, that although intraoperative and postoperative cardiovascular complications are higher in patients diagnosed with pheochromocytoma, such findings are no different than those from the open approach (6, 7). In fact, studies have shown that the rate of cardiovascular complications is lower with laparoscopy (7). One reason for the improvement is that laparoscopic mobilization of a pheochromocytoma allows the surgeon to "resect the patient from the tumor" and thereby minimizes catecholamine release. Hence, it is generally accepted that the laparoscopic approach is a safe and effective way to remove pheochromocytomas (1, 3 – 7).

Endoscopic Endocrine Surgery in the Neck

Endoscopic endocrine surgery in the neck became a viable surgical option in 1996 with the description of the first endoscopic parathyroidectomy by Gagner and associates (8). Continued research by surgeons around the world has resulted in descriptions of different operative approaches, relative and absolute contraindications, and recommendations about which patients would benefit most from these minimally invasive techniques. All would agree, however, that endoscopic endocrine surgery requires that the surgeon be familiar with open endocrine surgery and have the advanced laparoscopic skills necessary to perform the procedure safely.

Minimally Invasive Parathyroid Surgery

Improvements in preoperative localization and the availability of intraoperative parathyroid hormone (PTH) monitoring have significantly changed the approach to parathyroid surgery (9). A focused approach is indicated for patients with primary, sporadic hyperparathyroidism and a single adenoma depicted on preoperative imaging. The three preferred techniques utilize preoperative localization with ultrasound and/or sestamibi scan and intraoperative use of a rapid PTH assay (8 – 16). The radiographic localization studies all contribute important information to the surgeon. Ultrasound can provide specific anatomic information and help delineate other thyroid pathology, whereas the sestamibi scan can confirm the position of the adenoma, and localize lesions present in the mediastinum. The intraoperative PTH assay is also critical to the success of minimally invasive surgery. This test, which is performed in the operating room, analyzes the PTH level preoperatively, upon manipulation of the gland, and 5, 10, and 30 minutes after excision. If there is a 50% reduction in the preoperative PTH level, then the operation is completed. If, however, the appropriate decrease is not obtained, then a bilateral neck exploration is performed (9).

The three minimally invasive techniques used for parathyroid surgery are the video-assisted technique introduced by Miccoli, the endoscopic approach described by Gagner, which uses continuous CO_2 insufflation, and the unilateral neck exploration performed under local anesthesia (8, 10, 12). Each of these approaches has its own advantages and disadvantages. Both the video-assisted and endoscopic techniques require general anesthesia and are associated with longer operative times. On the other hand, the cosmetic result and visibility obtained with the magnifying laparoscope are advantageous. In addition, the endoscopic techniques can be utilized for bilateral or mediastinal exploration (8, 10, 12). The unilateral approach is performed through small, cosmetically acceptable incisions and is associated with shorter operative times. In addition, this procedure can be performed under local anesthesia and often on an outpatient basis. Unfortunately, this technique does not provide the visibility obtained with the endoscope, and if the PTH assay does not decrease adequately, then an open bilateral exploration becomes necessary (9).

Endoscopic Thyroid Surgery

Endoscopic thyroidectomy has been studied in small consecutive groups of patients and compared to conventional surgery (12, 18, 19). Two techniques have been described: the video-assisted technique described by Miccoli and the endoscopic technique described by Gagner and Inabnet (16–18). Both methods have been utilized successfully in the subset of patients with thyroid pathology amenable to the endoscopic approach. In some reports, the use of CO_2 in the neck has been shown to result in hypercarbia and respiratory acidosis (20). Fortunately, when encountered, it has resolved with no significant sequelae. In fact, Ochiai et al. report five cases of endoscopic thyroidectomy where hypercarbia was not encountered, when CO_2 insufflation pressures were maintained around 6 mm Hg (21).

Regardless of the method chosen, proponents of endoscopic thyroid surgery agree that appropriate patient selection is critical. All patients should undergo an adequate work-up, which includes thyroid function tests, ultrasound examination, and fine needle aspiration (FNA) (16). Patients with an FNA that shows atypia or other suspicious pathology should undergo an open procedure, because of the higher risk of malignancy. Currently, patients with a diagnosis of thyroid carcinoma are not candidates for endoscopic surgery (17). The lesions most amenable to the minimally invasive approach include lesions that are follicular in origin (as determined by FNA), Hurthle cell tumors, indeterminate nodules, solitary toxic nodules and thyroid cysts (18). Other contraindications to this procedure include the size of the lesion, multinodular goiter, prior neck surgery, and a body habitus that would preclude adequate visibility with insufflation (e.g., morbidly obese patients with short, thick necks). Inabnet et al. suggest that the endoscopic approach not be utilized for lesions larger than 3 cm, for the limited working space in the neck decreases exposure (17).

Studies have shown improved cosmetic results and faster recovery time with the use of both endoscopic approaches. Neither, however, has led to a decrease in the use of analgesics postoperatively. Surgeons using this method have commented on the improved intraoperative visibility with use of the magnifying laparoscope (18, 19). Identification of the structures in the neck is always a major concern of the endocrine surgeon. Since these techniques facilitate such identification, they may result in a decrease in the morbidity associated with injury to major structures like the recurrent laryngeal nerve. One universal disadvantage is the prolonged operative time needed for this approach. This, however, should diminish as surgeons become more experienced in the utilization of endoscopy for thyroid surgery (17).

Laparoscopic Pancreatic Surgery

A decade prior to the universal acceptance of minimally invasive surgery for the treatment of benign gallbladder disease, diagnostic laparoscopy was utilized to investigate the pancreas (22). Throughout the 1990s, as laparoscopy was becoming popular for treatment of a variety of surgical diseases, laparoscopic pancreatic surgery was slowly being improved. Today there are some clear indications for minimally invasive pancreatic surgery, though the actual practice is limited by the need for experience in open pancreatic surgery and expertise in advanced laparoscopic technique. Although this field continues to develop, laparoscopic pancreatic surgery is an already effective and reliable approach in defined clinical scenarios.

Diagnostic laparoscopy is an important adjunct to the treatment of pancreatic malignancy. Although not recommended for surgical ablation of disease, its use in determining resectability is critical. One of the most important diagnostic modalities used in the work-up of a patient with suspected malignancy is the CT scan. This modality is very accurate when determining unresectability; however, it has been less effective in determining resectability (23, 24). Laparoscopy, when utilized in the face of an indeterminate radiologic study, can decrease the morbidity associated with a laparotomy and extensive dissection. Before surgeons became more adept in laparoscopic technique, the ability to determine resectability was less than 50%, which is worse than with CT scan alone (23). However, as laparoscopic skill improved, diagnostic techniques developed to include more extensive dissection of critical areas. Such advances in technique have led to visualization of the celiac axis, hepatic artery, superior mesenteric vein and superior mesenteric artery, and even biopsy of the celiac, portal and perigastric nodes (23, 25). In addition, the use of intraoperative ultrasound has added another modality to diagnostic laparoscopy, and has been shown to increase the accuracy of determining resectability (26). Although this modality is operator dependent, when used by properly trained personnel it can offer a clear advantage. Even with the recent advances in spiral CT scans, diagnostic laparoscopy with intraoperative ultrasound seems to offer a more accurate means of determining resectability.

When unresectability is determined via radiographic or surgical means, laparoscopy can be utilized for palliative treatment (25–28). Since life expectancy is short when metastatic pancreatic cancer is diagnosed, decompression of the biliary obstruction may be palliative with the placement of stents. However, when complications develop following stent placement, or the endoscopist is unable to place the device, then surgical decompression becomes necessary. In addition, obstruction of the gastric outlet by the tumor may require surgical intervention. Laparoscopic biliary decompression and gastric/duodenal decompression are well described in the literature (27, 28). The most common method of biliary decompression is cholecystojejunostomy, for this procedure is faster and more technically feasible than choledochojejunostomy. Gastric outlet obstruction is treated with a gastrojejunostomy. Rhodes et al. point out in their study that the decreased length of hospital stay and faster recovery time offer a distinct advantage to this patient population. They performed the procedure in patients with complications from biliary stents, those with gastric outlet obstruction, and those found to have unresectable disease while undergoing diagnostic laparoscopy for what was thought to be resectable disease. The procedure was successfully completed in 15 of 16 patients. The length of the procedure averaged 75 minutes, and 14 of 16 patients were discharged within 7 days (28). Laparoscopy, when indicated and feasible, clearly offers an advantage when surgical treatment is necessary.

Laparoscopy has also been utilized for the internal drainage of persistent, large pancreatic pseudocysts. Both laparoscopic cystogastrostomy and cystojejunostomy have been described, with the former being more common (29). Different approaches to this disease have been described. One approach permits access to the posterior stomach via an enterostomy in the anterior stomach. This procedure has had good results, although it requires two gastrostomies. The other method approaches the posterior stomach through the gastrocolic ligament inferiorly. Although technically more challenging, this procedure is equally effective (25). Laparoscopic drainage of pseudocysts offers the advantage of a definitive procedure without the morbidity of laparotomy in an inherently sicker population.

Finally, laparoscopic pancreatic resection has been described for both benign neoplasms and chronic pancreatitis. Benign cystadenomas and endocrine tumors, particularly insulinomas, can be effectively treated by either enucleation or distal pancreatectomy, with or without splenectomy (26, 30–32). In addition, distal pancreatic resection for intractable pain associated with chronic pancreatitis has shown favorable results, although this procedure typically requires a splenectomy, because of the extensive retroperitoneal fibrosis associated with this disease process (30). Patterson et al. looked at a single-institution review of 19 pancreatic resections (32). In that study, 2 of the 19 were converted to open procedures, one for bleeding and the other for suspicion of malignancy. A pancreatic fistula complicated 16% of the cases, which is comparable to results with the open technique. Overall, it appears that the hospital length of stay is shorter and the recovery time is faster for laparoscopic patients (32). As with all advanced laparoscopic techniques, enucleation of endocrine tumors and distal pancreatectomy are safe and effective surgical treatment options for patients with pancreatic disease when performed by surgeons with the necessary experience and laparoscopic skills.

References

1. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. N Engl J Med 1992; 327:1033.
2. Clark O, Duh Q. Textbook of endocrine surgery. W.B. Saunders Company; 1997.
3. Prinz R. A comparison of laparoscopic and open adrenalectomies. Arch Surg 1995; 130:489–494.
4. Gagner M, Breton G, Pharand D, Pomp A. Is laparoscopic adrenalectomy indicated for pheochromocytomas? Surgery 1996; 120(6):1076–1079.
5. Gagner M, Pomp A, Heniford BT, et al. Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. Ann Surg 1997; 226(3):238–247.
6. Mobius E, Nies C, Rothmund M. Surgical treatment of pheochromocytomas: laparoscopic or conventional? Surg Endosc 1999; 13:35–39.
7. Edwin B, Kazaryan AM, Mala T, et al. Laparoscopic and open surgery for pheochromocytoma. BMC Surg 2001; 1:2.
8. Gagner M. Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism. Br J Surg 1996; 83:875.
9. Inabnet WB 3rd, Dakin GF, Haber RS, et al. Targeted parathyroidectomy in the era of intraoperative parathormone monitoring. World J Surg 2002; 26:921–925.
10. Miccoli P, Berti P, Conte M, et al. Minimally invasive video-assisted parathyroidectomy: lesson learned from 137 cases. J Am Coll Surg 2000; 191(6):613–618.
11. Henry J, Iacobone M, Mirallie E, et al. Indications and results of video-assisted parathyroidectomy by a lateral approach in patients with primary hyperparathyroidism. Surgery 2001; 130(6):999–1004.
12. Miccoli P, Bendinelli C, Vignali E, et al. Endoscopic parathyroidectomy: report of an initial experience. Surgery 1998; 124(6):1077–1079.
13. Gauger PG, Reeve TS, Delbridge LW. Endoscopically assisted, minimally invasive parathyroidectomy. Br J Surg 1999; 86:1563–1566.
14. Hallfeldt KK, Trupka A, Gallwas J, Horn K. Minimally invasive video-assisted parathyroidectomy. Surg Endosc 2001; 15:409–412.
15. Howe JR. Minimally invasive parathyroid surgery. Surg Clin North Am 2000; 80(5):1399–1426.
16. Inabnet W, Addis M. Endoscopic thyroidectomy with CO2 insufflation. Operative Techniques in Otolaryngology — Head and Neck Surgery 2002; 13:242–243.
17. Inabnet WB, Gagner M. Endoscopic thyroidectomy. J Otolaryngol 2001; 30(1):41–42.
18. Gagner M, Inabnet WB 3rd. Endoscopic thyroidectomy for solitary thyroid nodules. Thyroid 2001; 11(2):161–163.
19. Yeh TS, Jan YY, Hsu BR, et al. Video-assisted endoscopic thyroidectomy. Am J Surg 2000; 180:82–85.
20. Gottlieb A, Sprung J, Zheng XM, Gagner M. Massive subcutaneous emphysema and severe hypercarbia in a patient during endoscopic transcervical parathyroidectomy using carbon dioxide insufflation. Anesth Analog 1997; 84:1154–1156.
21. Ochiai R, Takeda J, Noguchi J, et al. Subcutaneous carbon dioxide insufflation does not cause hypercarbia during endoscopic thyroidectomy. Anesth Analg 2000; 90:760–762.
22. Meyer-Burg J, Ziegler U, Kirstaedter H. Peritoneoscopy in carcinoma of the pancreas: report of 20 cases. Endoscopy 1973; 5:86–90.
23. Conlon KC, Dougherty E, Klimstra DS, et al. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg 1996; 223(2):134–140.
24. Freeny PC, Traverso LW, Ryan JA. Diagnosis and staging of pancreatic adenocarcinoma with dynamic computed tomography. Am Coll Surg 1993; 165:600–606.
25. Park A, Schwartz R, Tandan V, Anvari M. Laparoscopic pancreatic surgery. Am J Surg 1999; 177:158–163.
26. Underwood RA, Soper NJ. Current status of laparoscopic surgery of the pancreas. J Hepatobiliary Pancreat Surg 1999; 6:154–164.
27. Shimi S, Banting S, Cuschieri A. Laparoscopy in the management of pancreatic cancer: endoscopic cholecystojejunostomy for advanced disease. Br J Surg 1992; 79:317–319.
28. Rhodes M, Nathanson L, Fielding G. Laparoscopic biliary and gastric bypass: a useful adjunct in the treatment of carcinoma of the pancreas. Gut 1995; 36:778–780.
29. Mori T, Abe N, Sugiyama M, et al. Laparoscopic pancreatic cystogastrostomy. J Hepatobiliary Pancreat Surg 2000; 7(1):28–34.
30. Cuschieri SA, Jakimowicz JJ. Laparoscopic pancreatic resections. Semin Laparosc Surg 1998; 5(3):168–179.
31. Gagner M, Gentileschi P. Hand-assisted laparoscopic pancreatic resection. Semin Laparosc Surg 2001; 8(2):114–125.
32. Patterson EJ, Gagner M, Salky B, et al. Laparoscopic pancreatic resection: single-institution experience of 19 patients. J Am Coll Surg 2001; 193(3):281–287.

Emergency Prophylaxis Following Needle-Stick Injuries and Sexual Exposures:

Results from a Survey Comparing New York Emergency Department Practitioners with their National Colleagues

ROLAND C. MERCHANT, M.D., M.P.H., AND REZA KESHAVARZ, M.D., M.P.H.

Abstract

Background: Emergency prophylaxis following needle-stick and sexual exposures includes HIV post-exposure prophylaxis, hepatitis B prophylaxis and emergency contraception. The Centers for Disease Control and Prevention endorse HIV post-exposure and hepatitis B prophylaxis for health care workers, and hepatitis B prophylaxis and emergency contraception after sexual assault. The New York State Department of Health advocates HIV post-exposure prophylaxis after sexual assault. This study compares emergency department practitioners in New York State (NYS) with those from other states in their willingness to offer emergency prophylaxis after needle-stick and sexual exposures, and their self-reported history of prescribing and using HIV post-exposure prophylaxis.
Methods: The authors surveyed emergency department practitioners from across the US at the American College of Emergency Physicians 2000 Scientific Assembly. The questionnaire included clinical scenarios describing different patients who present to the emergency department within one hour of a needle-stick injury, sexual assault or consensual sexual encounter, and had questions on the practitioners' self-reported prescribing and usage of HIV post-exposure prophylaxis. For each scenario the practitioners were asked to indicate if they would offer emergency prophylaxis to different patients at varied HIV risk levels. The data were processed through SPSS 10.0.
Results: Of the 600 respondents, 100 were from NYS. In the clinical scenarios, NYS practitioners were more likely than other US practitioners to offer HIV post-exposure prophylaxis for exposures to unknown and low HIV risk sources ($p<0.05$) and to offer hepatitis B prophylaxis in most of the sexual exposure scenarios ($p<0.01$). All practitioners offered HIV post-exposure and hepatitis B prophylaxis less often after consensual sexual encounters than after sexual assault and needle-stick injuries. In most cases, NYS practitioners were more willing to offer emergency contraception after sexual assault and consensual sexual encounters than were other practitioners ($p<0.05$). In terms of self-reported prescribing of HIV post- exposure prophylaxis, NYS practitioners had prescribed HIV post-exposure prophylaxis after sexual assault ($p<0.001$) and non-health-care-worker needle-stick injuries ($p<0.05$) much more often than did other practitioners.
Conclusions: Compared to their national colleagues, NYS emergency department practitioners were generally more willing to offer all forms of emergency prophylaxis after sexual assault. They also reported having had more experience than other practitioners in prescribing HIV post-exposure prophylaxis. Although most practitioners were clearly willing to offer HIV post-exposure prophylaxis for nonoccupational exposures, NYS practitioners were less willing to offer emergency prophylaxis following consensual sex than after sexual assault. These findings suggest that the NYS guidelines for HIV post-exposure prophylaxis after sexual assault may have influenced emergency practitioners' willingness to offer and prescribe prophylaxis.
Key Words: HIV post-exposure prophylaxis, hepatitis B prophylaxis, emergency contraception, post-exposure prophylaxis, sexual assault, needle-stick injuries.

Introduction

EMERGENCY PROPHYLAXIS following needle-stick injuries and sexual exposures includes HIV post- exposure prophylaxis (HIV PEP), hepatitis B prophylaxis, and emergency contraception. These procedures are recommended by various authorities under certain conditions.

There are two types of HIV PEP: occupational and nonoccupational. Occupational HIV PEP is given to health care workers who have possibly been exposed to HIV while on the job; nonoccupational HIV PEP is for all other patients who have possibly been exposed to HIV due to needle-stick injuries, drug injections, sexual assault or consensual sex. The Centers for Disease Control and Prevention (CDC) first established guidelines on occupational HIV PEP in 1996; these were updated in 2001 (1). However, the CDC has not issued guidelines for nonoccupational HIV PEP. In 1998, New York became the first state to issue guidelines for

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Roland C. Merchant, M.D., M.P.H...Section of Emergency Medicine and Division of Infectious Diseases, Brown University School of Medicine, Rhode Island Hospital, 593 Eddy Street, Davol 141, Providence, RI 02903; email: rmerchant@lifespan.org

This study was presented at the First Annual New York State Region Society for Academic Emergency Medicine meeting, March 2001, in Rochester, NY.

Accepted for publication June 2003.

HIV PEP following adult and adolescent sexual assault, and was the only state with such guidelines at the time of this survey (2). The impact of these guidelines on medical practice in New York has not been studied.

The CDC endorses the use of hepatitis B prophylaxis for non-immune, uninfected patients who have had possible needle-stick or sexual exposures to hepatitis B (1, 3), and recommends emergency prophylaxis following sexual assault. The American College of Obstetricians and Gynecologists encourages the use of emergency contraception to prevent unwanted pregnancy after sexual assault and consensual sex (4). The American College of Emergency Physicians recommends its use after sexual assault (5).

Emergency departments (EDs) are locations where emergency prophylaxis is likely to be considered, given the immediate need for evaluation and treatment of patients who sustained needle-stick and sexual exposures. Through a national survey, we compared both New York State (NYS) and national ED practitioners' willingness to offer emergency prophylaxis, as well as their self-reported experience with prescribing and using HIV PEP. The survey was designed to determine if, as a result of NYS HIV PEP guidelines for sexual assault, NYS practitioners were more likely to prescribe all forms of emergency prophylaxis.

Materials and Methods

The authors created an anonymous, voluntary, written questionnaire regarding emergency prophylaxis, for use at a national emergency medicine conference of ED practitioners. The questionnaire was initially tested on a small cohort of practitioners at The Mount Sinai Hospital. The questionnaire included: (a) practitioner demographic questions; (b) clinical scenarios describing seven different patients who present to the ED within one hour of a needle-stick injury, sexual assault, or consensual sexual encounter; and (c) questions on the practitioners' self-reported prescribing and use of HIV PEP for themselves. (The Mount Sinai School of Medicine Institutional Review Board had approved the study.)

For each clinical scenario, the practitioners were asked to indicate if they would offer emergency prophylaxis (HIV PEP, hepatitis B prophylaxis, and emergency contraception) to different patients (health care worker or non-healthcare worker adult or child) after specific exposures (needle stick, sexual assault or consensual sex) and varied HIV risk levels (unknown, HIV infected, high HIV risk factors — defined as injecting drug use, male-male sex, prostitution — or low HIV risk factors). In order to mimic the information typically known on initial ED presentation, the questionnaire specified that no further information was available (i.e., the source could not be tested or queried). The questionnaire also stated that each exposure was significant (e.g., bloody needle-stick or unprotected sexual intercourse) and each patient was an ideal prophylaxis candidate (not pregnant, not HIV infected, and not hepatitis B immune or infected). Patient presentation within one hour was specified for all exposures, so that prophylaxis decisions would not be made regarding time elapsed from exposure to ED presentation.

The full survey was conducted at the American College of Emergency Physicians 2000 Scientific Assembly in Philadelphia, Pennsylvania. More than 4,000 health care practitioners attended the meeting. All ED practitioners who could prescribe medications (physicians, nurse practitioners, and physician assistants) and who visited the survey booth in the exhibition hall were asked to complete a questionnaire. ED practitioners were offered the chance to enter a $100 gift certificate lottery if they completed a questionnaire. One of the authors was available to answer or clarify questions.

The data were abstracted from the questionnaires and entered into SPSS 10.0 (SPSS Corporation, Chicago, IL, 1999). Only surveys which were more than 90% complete were used. The statistical analyses in SPSS 10.0 included generation of point estimates of proportions and comparisons of proportions between NYS and national ED practitioners, using the Pearson's Chi square test.

Results

There were 600 respondents. An additional 15 surveys were not used because of marking errors and incomplete responses. One hundred of the respondents were from NYS: 63% male, 37% female (vs. 71% and 29%, respectively, nationally); 32% academic attending, 17% community, and 41% resident physicians (vs. 33% nationally); and 11% nurse practitioners and physician assistants. Of the academic and community physicians, 54% were board certified or eligible in emergency medicine.

Table 1 summarizes practitioner responses to the clinical scenarios. Table 2 displays the

TABLE 1

Comparison of the Use of Emergency Prophylaxis by NYS ED and Those from Other States

Needle-Stick Injuries

Summary of 600 responses to survey question: "A (health care worker, adult, or 5-year-old child) is stuck by a bloody needle from (an unknown source, an HIV-positive source, a source with high-HIV-risk factors, or a source with low-HIV-risk factors). Indicate the kind of prophylaxis you would offer, if any."

	HIV Risk of the Exposure Source	NYS ED Practitioners Offering HIV PEP (n=100)	Other US ED Practitioners Offering HIV PEP (n=500)	p-value	NYS ED Practitioners Offering Hepatitis B Prophylaxis (n=100)	Other US ED Practitioners Offering Hepatitis B Prophylaxis (n=500)	p-value
Health Care Worker	unknown	89%	68%	0.007	94%	87%	0.052
	HIV infected	96%	98%	0.170	94%	86%	0.030
	high risk	96%	95%	0.670	93%	87%	0.092
	low risk	59%	38%	0.001	82%	67%	0.003
Non-Health Care Adult	unknown	87%	76%	0.017	92%	99%	0.241
	HIV infected	96%	97%	0.437	94%	91%	0.331
	high risk	97%	94%	0.257	95%	89%	0.05
	low risk	51%	38%	0.014	81%	67%	0.00
5-year-old	unknown	83%	73%	0.041	90%	84%	0.15
	HIV infected	93%	95%	0.377	91%	86%	0.21
	high risk	92%	92%	0.869	92%	86%	0.09
	low risk	52%	35%	0.002	78%	63%	0.00

Sexual Assault

Summary of 600 responses to survey question: "An adult/a 5-year-old child is sexually assaulted with unprotected intercourse from (an unknown assailant, an HIV-positive assailant, an assailant with high-HIV-risk factors, or an assailant wit low-HIV-risk factors). Indicate the kind of prophylaxis you would offer, if any."

	HIV Risk of the Exposure Source	NYS ED Practitioners Offering HIV PEP (n=100)	Other US ED Practitioners Offering HIV PEP (n=500)	p-value	NYS ED Practitioners Offering Hepatitis B Prophylaxis (n=100)	Other US ED Practitioners Offering Hepatitis B Prophylaxis (n=500)	p-value	NYS ED Practitioners Offering Emergency Contraception (n=100)	Other US ED Practitioners Offering Emergency Contraception (n=500)	p-valu
Adult	unknown	87%	70%	0.001	92%	75%	0.000	96%	87%	0.00
	HIV infected	96%	96%	0.846	93%	82%	0.007	96%	89%	0.03
	high risk	96%	93%	0.275	93%	82%	0.006	96%	88%	0.01
	low risk	67%	89%	0.001	80%	61%	0.000	87%	78%	0.05
5-year-old	unknown	87%	72%	0.002	88%	77%	0.017			
	HIV infected	92%	95%	0.280	88%	80%	0.056			
	high risk	91%	91%	0.972	93%	80%	0.002			
	low risk	54%	36%	0.001	76%	58%	0.001			

continu

self-reported prescribing experience with HIV PEP of practitioners from NYS and other states.

HIV Post-exposure Prophylaxis

Willingness to prescribe HIV PEP. In the clinical scenarios describing needle-stick injuries, sexual assault and consensual sexual encounters, NYS and other US ED practitione said that they would offer HIV PEP equally often for exposures to HIV-infected and hig HIV-risk individuals. NYS ED practitione were more likely to offer HIV PEP for exp sures to unknown and low-HIV-risk source There was a trend among NYS ED practitione toward offering HIV PEP more often after sexu

TABLE 1 *Continued from previous page*

Consensual Sex

Summary of 600 responses to survey question: "An adult / a 15-year-old engaged in unprotected intercourse (NOT an assault) with (an unknown person, an HIV-positive person, a person with high-HIV-risk factors, or a person with low-HIV-risk factors). Indicate the kind of prophylaxis you would offer, if any."

	HIV Risk of the Exposure Source	NYS ED Practitioners Offering HIV PEP (n=100)	Other US ED Practitioners Offering HIV PEP (n=500)	p-value	NYS ED Practitioners Offering Hepatitis B Prophylaxis (n=100)	Other US ED Practitioners Offering Hepatitis B Prophylaxis (n=500)	p-value	NYS ED Practitioners Offering Emergency Contraception (n=100)	Other US ED Practitioners Offering Emergency Contraception (n=500)	p-value
Adult	unknown	68%	41%	0.001	73%	47%	0.000	87%	68%	0.000
	HIV infected	92%	88%	0.288	83%	70%	0.007	93%	76%	0.000
	high risk	89%	83%	0.141	84%	69%	0.003	91%	73%	0.000
	low risk	41%	18%	0.001	57%	37%	0.000	74%	58%	0.003
15-year-old	unknown	66%	43%	0.001	69%	50%	0.001	84%	71%	0.009
	HIV infected	87%	87%	0.918	82%	70%	0.021	90%	76%	0.002
	high risk	85%	82%	0.523	83%	69%	0.006	89%	74%	0.001
	low risk	33%	19%	0.001	54%	37%	0.002	79%	59%	0.000

TABLE 2

HIV PEP Prescribing Patterns of ED Practitioners from New York State versus Those from Other States

	New York	Other States	p-value
ED practitioners reporting ever having prescribed HIV PEP	86%	54%	0.000
Exposures for which ED practitioners report having prescribed HIV PEP			
Sexual assault	69%	43%	0.000
Health care worker needle-sticks	89%	92%	0.384
Non-health-care-person needle-sticks	60%	46%	0.022
Consensual sex	12%	6%	0.098
ED practitioners who have prescribed HIV PEP for patients under age 18	26%	17%	0.073
Exposures for which HIV PEP was given			
Sexual assault	64%	72%	0.491
Health care worker needle-sticks	9%	8%	0.822
Non-health-care-person needle-sticks	46%	25%	0.074
Consensual sex	5%	2%	0.517
ED practitioners who have used HIV PEP for themselves	16%	9%	0.078
Exposures for which HIV PEP was taken			
Sexual assault	6%	6%	0.957
Occupational needle-stick	94%	90%	0.650

encounters with these two sources than after needle-stick injuries. All practitioners offered HIV PEP more often after exposures to known HIV-infected and high-risk sources than to unknown and low-risk sources for all patients and exposures. All practitioners also offered HIV PEP less often after consensual sexual encounters than after sexual assault and needle-stick injuries.

Self-reported prescribing of HIV PEP. NYS ED practitioners prescribed HIV PEP after sexual assault and non-health-care worker needle-stick injuries much more often than did other US ED practitioners. The difference was even greater for sexual assault survivors. NYS ED practitioners reported equal experience with HIV PEP in all other areas: needle-stick injuries among health care workers, sexual and needle-stick exposures among adolescents and children, and self-use of HIV PEP.

Hepatitis B Prophylaxis

For the clinical scenarios describing needle-stick injuries, both groups offered hepatitis B prophylaxis to all patients equally often for exposures involving HIV-infected and high-HIV-risk sources. NYS ED practitioners offered hepatitis B prophylaxis more often than other US practitioners for unknown and low-risk sources. NYS ED practitioners generally offered hepatitis B prophylaxis more often for individuals after sexual exposure. As was true for HIV PEP, all practitioners offered hepatitis B prophylaxis more often after needle-stick injuries and sexual assault than after consensual sex, and more often after exposures to known HIV-infected and high-risk sources than to unknown and low-risk sources.

Emergency Contraception

NYS ED practitioners were more willing to offer emergency contraception after sexual assault and consensual sexual encounters than were other US ED practitioners, particularly after consensual sex. All practitioners appeared to offer emergency contraception less often after exposures to low-HIV-risk sources than to all other sources.

Discussion

NYS ED practitioners surveyed were more likely to use HIV PEP and in some cases more willing to prescribe it than were respondents from other states. This difference could be due to several factors, including: (a) the existence of NYS guidelines on sexual assault HIV PEP; (b) provider recognition of the high prevalence of HIV in certain parts of NYS; and (c) the large percentage of resident physicians in our study who may be more inclined to use newer therapies or who have received more recent instructions on HIV PEP. The greater use of HIV PEP following sexual assault by NYS practitioners may attest to their knowledge and acceptance of the state guidelines.

HIV PEP following consensual sex is not yet endorsed by either the CDC (6) or the NYS Department of Health. It is anticipated that the NYS Department of Health will support its provision in an updated version of their HIV PEP guidelines (personal communication with the New York AIDS Institute). However, prior to and since this survey, multiple groups worldwide have advocated its usage (7 – 10). In brief, these groups recommend HIV PEP following consensual sexual assault if the potential recipient: (a) presents within 36 – 72 hours of the exposure; (b) the sexual exposure could result in HIV transmission (e.g., unprotected penile-vaginal intercourse with a male infected with HIV or at risk of HIV infection); and (c) the recipient commits to reducing further HIV risk-taking behavior.

Despite the existence of these recommendations, NYS ED practitioners were less inclined to offer HIV PEP for consensual sex exposures than for sexual assault. The reasons for this could include: (a) belief that HIV transmission is more likely following sexual assault; (b) greater awareness of NYS sexual assault guidelines; (c) local or hospital ED policies that endorse or dictate offering HIV PEP to sexual assault victims; (d) less awareness of HIV PEP recommendations for consensual sexual encounters; and (e) lack of state or national guidelines on HIV PEP after consensual sex. Additionally, some may still believe that seroconversion following consensual sex, unlike sexual assault, was "voluntary," and therefore "not worthy" of prophylaxis.

NYS ED practitioners were more willing to offer hepatitis B prophylaxis for sexual assault than were their national counterparts, especially in comparison to needle-stick injuries. Since hepatitis B prophylaxis is recommended in the NYS HIV PEP sexual assault guidelines, it is possible that the guidelines may have increased the willingness of NYS ED practitioner to offer hepatitis B prophylaxis in the clinical scenarios (2).

Although emergency contraception is not mentioned in the NYS HIV PEP guidelines NYS ED practitioners were much more willing to offer emergency contraception than were ED practitioners from other states. This distinction was even greater for the consensual sex scenarios. The reason for this difference is unclear but may be due to matters of local practice or be an indirect effect of the guidelines. NYS ED practitioners, like other state practitioners, were more willing to offer emergency contraception based on HIV risk. This may reflect a viewpoint that sexual encounters that pose higher HIV risk are more deserving of contraception.

Our study had several limitations, including: (a) small sample size, which may have reduced our ability to show differences among practitioners; (b) a possibility that the survey did not reflect the composition of NYS or other emergency department (e.g., the large percentage of resident physicians, the convenience sample format, and the lack of an accounting of the respondent' practice location within the state); and (c) a reliance upon the respondents' recall of therapies employed, which may not be accurate. We hope that further studies may expand on our work and overcome these limitations. Furthermore, we recognize that actual practice may differ from the practitioners' expressed willingness to offer emergency prophylaxis.

Conclusion

We found that a very high percentage of NYS ED practitioners surveyed had prescribed HIV PEP– a percentage higher than the national average. Possibly because of the NYS Department of Health HIV PEP sexual assault guidelines, NYS ED practitioners were generally more likely than their national counterparts to offer all forms of emergency prophylaxis after sexual assault. Like their national colleagues, fewer NYS ED practitioners were willing to consider consensual sexual exposures as equal to sexual assault as a valid reason for emergency prophylaxis. We therefore recommend that the NYS Department of Health expand their guidelines to include consensual sexual exposures for at-risk persons and reinforce the need for hepatitis B prophylaxis and emergency contraception. We also advocate more training for all practitioners on these issues.

References

1. Centers for Disease Control. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for post-exposure prophylaxis. MMWR Morb Mortal Wkly Rep 2001; 50(RR11):1–42.
2. AIDS Institute. HIV prophylaxis following sexual assault: guidelines for adults and adolescents. New York (NY): AIDS Institute, New York State Department of Health; 1998.
3. Centers for Disease Control. 1998 Guidelines for the treatment of sexually transmitted diseases. MMWR Morb Mortal Wkly Rep 1998; 47(RR1)1–118.
4. American College of Obstetricians and Gynecologists. ACOG practice patterns: emergency oral contraception. Int J Gynaecol Obstet 1997; 56:290–297.
5. American College of Emergency Physicians. Evaluation and management of sexually assaulted or sexually abused patients. Dallas (TX): ACEP, 1999. Available at: http://www.acep.org/library/pdf/sxa_handbook.pdf
6. Centers for Disease Control. Management of possible sexual, injecting-drug-use, or other nonoccupational exposure to HIV, including considerations related to antiretroviral therapy. Public Health Service statement. MMWR Morb Mortal Wkly Rep 1998; 47(RR17):1–14.
7. Katz MH, Gerberding JL. Management of occupational and nonoccupational postexposure HIV prophylaxis. Curr Infect Dis Rep 2002; 4(6):543–549.
8. Merchant RC, Mayer KH, Browning CA. Nonoccupational HIV post-exposure prophylaxis: guidelines for Rhode Island from the Brown University AIDS Program and the Rhode Island Department of Health. Med Health R I 2002; 85(8):244–248.
9. Bani-Sadr F, Teissiere F, Curie I, et al. Anti-infection prophylaxis after sexual assault. Experience of the Raymond Poincare-Garches Hospital [French, with English abstract]. Presse Med 2001; 30(6):253–258.
10. Correll P, Smith D, Grulich A. Post-exposure prophylaxis for non-occupational exposure to HIV: experience in New South Wales one year after the introduction of the guidelines. N S W Public Health Bull 2000; 11(7):113–118.

Controversies in Differentiating Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Neelam T. Shah, M.D.[1]*, and Jacob H. Rand, M.D.[2]**

Abstract

The diagnoses of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) often remain questionable, forcing the clinician to make the difficult decision of initiating therapy based on symptomatology and clinical judgment and, sometimes, instinct. An increased awareness of characteristic symptoms and early diagnoses of TTP and HUS are of utmost importance, given the excellent results obtained with prompt plasma exchange therapy. Tremendous progress has been made in understanding TTP and HUS since TTP was first described more than 75 years ago at Mount Sinai. However, several questions are still not definitively answered. In this article, we will review background on both entities, and then describe the controversy in differentiating between them.

Key Words: Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome.

In 1924, Dr. Eli Moschcowitz, of The Mount Sinai Hospital, published the first case study of a young woman with "an acute febrile pleomorphic anemia with hyaline thrombosis of the terminal arterioles and capillaries"; she died after two weeks (1). Her illness was characterized by fever, bleeding, neurologic and renal abnormalities and a microangiopathic hemolytic anemia. This syndrome subsequently became known as Moschcowitz's disease, or "thrombotic thrombocytopenic purpura (TTP)." Thirty years later, a similar illness was described in children and named hemolytic uremic syndrome (HUS) (2).

The clinical and pathophysiologic relationship between these two entities has been discussed and debated for more than 40 years. In this article, we will review some background on both entities, and then describe the controversy in differentiating between them.

Epidemiology

In the United States, approximately 1,000 new cases of TTP are diagnosed each year, with women affected twice as often as men. Most patients range in age from 20–60; the disease is uncommon in the elderly and in infants. Although the majority of patients with TTP have no known clearly associated risk factor, it may occur in the third trimester of pregnancy or as an adverse reaction to some medications, and has been associated with autoimmune disorders (3).

There are two primary types of TTP: the single acute episode and chronic relapsing TTP. The acute episode is much more common and severe. Two-thirds of patients experience a single episode which does not recur after recovery. For the remaining one-third, the disease recurs intermittently. Chronic relapsing TTP is a much rarer entity, with approximately 25 patients in all of North America in 1996. It occurs with frequent episodes at regular intervals, every 3–4 weeks, and usually occurs in children (4).

Two types of HUS have been described (5). Diarrhea-associated HUS occurs most com-

---

[1] Fellow, Hematology/Oncology and [2] Professor of Medicine and Pathology, Thrombosis and Hemostasis Section, Mount Sinai School of Medicine, New York, NY.

Presently working at *Memorial Sloan Kettering Cancer Center, New York, NY and **Albert Einstein College of Medicine, Montefiore Medical Center Campus, Bronx, NY.

Address all correspondence to Jacob H. Rand, M.D., Professor of Pathology and Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Core Laboratory Office - North Pavilion 8, 111 East 210th Street, Bronx, NY 10467.

Accepted for publication April 2003.

monly in children epidemically in the first two years of life, and it is usually self-limited. The majority of these cases have been associated with a bloody diarrhea prodrome secondary to *Escherichia coli* 0157:H7. Sporadic, nondiarrhea-associated HUS is seen more commonly in adults and is sometimes associated with a mild viral prodrome. We will focus more on this nondiarrhea type of HUS, as this is the entity which is difficult to distinguish from TTP.

TTP is characterized by the typical findings of severe thrombocytopenia (usually less than 10,000 platelets/mm^3 in acute episode), hemolytic anemia, schistocytosis, and polychromasia; central nervous system ischemia and neuropathy, may range in severity from transient bizarre mentation and behavior to sensory-motor deficits, aphasia, seizures, or coma; fever, which occurs in only a minority of patients; and renal abnormalities, with hematuria and/or proteinuria. Renal failure is rare. Symptoms of ischemia in the gastrointestinal circulation, especially abdominal pain, have been recognized with increasing frequency (3).

The nondiarrhea form of HUS is defined by the triad of acute renal failure, intravascular hemolysis, and thrombocytopenia. Severe renal dysfunction is a prominent feature and often requires dialysis. Thrombocytopenia, hemolytic anemia, and LDH elevations are present but are usually less profound in HUS than in TTP. In addition, HUS is frequently associated with hypertension. Mortality for HUS is much lower than for TTP (5).

Because TTP can sometimes involve severe renal disease and HUS can involve extrarenal disease, the two disorders can be especially difficult to distinguish. Frequently, the same patient will be described as having HUS by nephrologists and TTP by hematologists.

Pathophysiology

The basic pathologic processes of TTP and HUS have been proposed to involve endothelial cell injury and the subsequent release of platelet-aggregating substances which result in the formation of thrombotic lesions in terminal arterioles and capillaries. The initial endothelial cell damage may involve apoptosis. Mitra et al. have shown that plasma from patients with TTP and nondiarrhea HUS induced apoptosis in human microvascular endothelial cells (6). Another group of investigators also provided support for this mechanism in demonstrating apoptosis of endothelial cells in spleens removed from patients with TTP (7).

The specific underlying cause of these thrombi has not been established. Various platelet-aggregating substances have been proposed and will be reviewed in this paper. These microvascular thrombi, which Moschcowitz described in his 16-year-old patient as "hyaline," were subsequently described by Asada and his group by immunohistochemical studies to be composed of aggregated platelets with an abundance of von Willebrand factor (vWF), but containing little fibrin (8).

The lesions of TTP are seen most commonly in the microvasculature of the brain, kidney, pancreas, heart, spleen, and adrenal glands, but can be found throughout the body, though less commonly in the lung or liver. The partial and complete occlusions in many organs, leading to organ failure, along with the consumptive thrombocytopenia, result in the clinical manifestations of TTP.

Although it is generally accepted that the thrombotic lesions give rise to the characteristic manifestations of TTP, the cause of the lesions remains unclear. They are believed to be the result of intrusion into the circulation of one or more platelet-aggregating substances. It is thought that platelet-aggregating factor p37, reported to induce clumping by binding to platelet glycoprotein IV (9), is derived from an infectious agent, and that normal patients and patients with TTP in remission develop antibodies to this infectious agent (10).

Calpain, a calcium-dependent cysteine protease (11), and cathepsin, a non-calcium-dependent cysteine protease (12), are thought to be released from either injured tissue or endothelial cells. Calpain is reported to proteolyze vWF multimers into fragments that can agglutinate platelets (11). This would, however, be unusual, given that proteolysis of vWF multimers into small fragments is commonly associated with loss of vWF-regulated platelet aggregation. vWF multimer abnormalities have recently been a focus of intense investigation in this disorder.

von Willebrand Factor

vWF monomers (270 kDa) form multimers of varying sizes via disulfide bridges (13). vWF multimers are produced within endothelial cells and megakaryocytes and are stored within the Weibel-Palade bodies of endothelial cells, which are the predominant source of vWF multimers, and the alpha granules of platelets.

Unusually Large vWF Multimers

In 1982, Moake and colleagues described unusually large multimers of vWF (ULvWF) in the plasma of patients with chronic relapsing TTP. They proposed that endothelial cells secreted these large multimers, which are even larger than the largest vWF multimers found in normal plasma. These ULvWFs were secreted retrograde into the subendothelium, and promoted platelet adhesion after vascular injury (14). A vWF-cleaving protease responsible for cleaving the large vWF multimers into the sizes seen in normal plasma has been identified in the platelet-poor plasma cryosupernatant portion of normal plasma. Deficiency or absence of this protease has been reported in TTP patients, but not in HUS patients (15). Fluid shear stress also appears to play a role in inducing platelet aggregation (16) (Table 1).

In 1989, Frangos et al. found a substance in cryosupernatant capable *in vitro* of reducing reversibly the size of ULvWF multimeric forms released by endothelial cells in culture into smaller vWF multimers ordinarily found in the circulation (17). This activity had characteristics of a limited disulfide bond reductase.

The mechanism was further clarified by Tsai in 1996 (18) and Furlan in 1997 (19), when they independently described a metal-containing proteolytic enzyme (metalloproteinase) in normal plasma, which could cleave the peptide bond between tyrosine at position 842 and methionine at position 843 in the monomeric vWF subunits, thereby degrading large multimers. This metalloproteinase can cleave vWF multimers *in vitro* if the forms are partially unfolded mechanically (as by shear stress) (20) or chemically (as by guanidine HCl) (18), or due to other chaotropic conditions such as low ionic strength or urea in the presence of divalent cations (19).

Hence, it is proposed that there is tandem action of the ULvWF reductase followed by a vWF metalloproteinase *in vivo*. It was proposed that the proteolysis prevented the reformation of ULvWF forms, which may occur *in vivo* in the absence of vWF metalloproteinase activity.

TABLE 1

Abnormalities of vWF Metabolism Proposed for TTP

Unusually large vWF multimers
Defective processing of multimers
Fluid shear stress

There is biochemical precedent for analogous tandem sequences of reductase-protease activities in human biology. In 1977, Stathakis et al. in Australia described the production of angiostatin by a disulfide bond reductase. Plasmin autoproteolysis follows and results in angiostatin fragments (21).

An important finding suggesting that the metalloproteinase has a role in normal physiology is that cleavage *in vitro* of vWF and ULvWF multimers results in the generation of 176 kD and 140 kD vWF fragments identical to those found in normal plasma (18).

Presumably in a patient with TTP, the high levels of shear stress caused by platelet thrombi in the circulation cause vWF unfolding and hence proteolysis. Therefore, the persistence of the ULvWF multimers in patients with acute TTP remains to be explained. A reasonable explanation to be offered is a defect in the proteolysis of the ULvWF which is the focus of the next series of investigations.

Defective Processing of Multimers

A potentially important finding was made in 1997, when Furlan et al. described 4 patients with chronic relapsing TTP who had deficiency of vWF-cleaving protease activity in plasma (22). This supported the hypothesis that the ULvWF multimers are responsible for the formation of platelet aggregates in the circulating blood. Because no inhibitor of the enzyme was found, the deficiency was thought to be congenital.

In 1998, two different groups, one led by Furlan (15) and another led by Tsai (23), published data on the pathogenesis of the more common type of TTP, characterized by a single acute episode. Tsai's evidence showed von Willebrand factor-cleaving protease deficiency in acute TTP. Inhibitors to the protease were found in 67% of plasma samples from the acute phase of disease. Tsai provided evidence, using affinity chromatography, that the inhibitor is an immunoglobulin G (IgG) antibody.

In their 1998 work, Furlan and associates presented a key finding regarding the inhibitor (15). They show the activity of vWF-cleaving protease and the level of its inhibitor in patients with nonfamilial TTP and HUS, and familia TTP and HUS. Plasma samples were collected during the acute event and in remission.

Most of the patients with acute nonfamilia TTP have some protease inhibitor preventing the breakdown of the multimers into smaller fragments, while in remission, they have some protease activity. In contrast, in the group of patients with nonfamilial HUS, there is no detectable inhibitor, consistent with breakdown of multimers. Patients with familial TTP were all found to have a protease deficiency of less than 5% of normal activity, but no inhibitor. In familial HUS, again, normal protease levels were found, without evidence of an inhibitor. Data from these two studies warrant further investigation into the role of protease level measurement in differentiating TTP from HUS. Recently, the von Willebrand factor-cleaving protease has been identified to be a marker of the ADAMTS (a disintegrin and metalloprotease with thrombospondin type 1 motif) zinc metalloprotease family, and is more specifically called ADAMTS13 (24). Several mutations of ADAMTS13 have been reported and found to have clinical correlation. Homozygous or doubly heterozygous ADAMTS13 mutations were found in patients clinically affected with TTP (25).

A link between the TTP and altered immune reactivity has been proposed, but as of yet, the reasons for the transient autoantibody production and the selective antigenic targeting of the protease are not known (26–28).

Ticlodipine, a platelet aggregation inhibitor, has also been associated with TTP, and it has recently been found that patients with ticlopidine-associated TTP have also acquired antibodies to the metalloproteinase (29).

Despite the progress made in understanding the pathophysiology of TTP, the complexity of this mechanism is attested to by the work of Moore et al. (30). In their study, they find that abnormalities in vWF-cleaving protease activity occur not only in a significant portion of patients with TTP, but also in patients with other thrombocytopenic disorders such as idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, and systemic lupus erythematosus. They concluded that abnormalities of vWF protease activity do not correlate completely with the presence of TTP.

Shear Stress

How do the ULvWF multimers aggregate platelets? Fluid shear stress (i.e., frictional forces generated by the relative parallel motion between fluid planes during flow) in the microcirculation may be important during episodes of TTP in promoting attachment of ULvWF multimers to shear-altered vWF receptors on platelets, which results in platelet aggregation (16).

Increased shear stress has been shown to promote platelet aggregation *in vitro* by stimulating ULvWF multimer binding to shear-altered glycoprotein Ib (GPIb) component of platelet GPIb-IX-V receptors. These multimers subsequently bind to GPIIb/IIIa on adenosine diphosphate (ADP)-activated platelets (31). Platelet aggregation requires binding of the multimers to both types of platelet receptors. Presumably, after small thrombi are formed in the microcirculation of TTP patients, there is further increased shear stress on the platelets in flowing blood and hence increased platelet aggregation (16, 31).

Chow et al. (32) performed flow cytometry on platelet aggregates from samples obtained from healthy and TTP patients. It was shown that after applying 90 dynes/cm^2 shear stress for 1 minute, there was an increase in both size and complexity, presumably representing the platelet aggregates. A study of a TTP patient showed that the platelet aggregation during the acute episode disappeared when the patient recovered. As mentioned earlier, Asada and his group performed immunohistochemical studies on these platelet aggregates which occluded microvessels and found them to contain vWF (8).

In summary, the pathophysiology of TTP appears to involve the ULvWF polymers synthesized by endothelial cells (33). Normally, these large vWF multimers undergo proteolysis in the high shear environment of the arterial circulation by the enzyme vWF metalloproteinase (top). Proteolysis reduces the size of the polymers and consequently inhibits their binding to platelet glycoprotein (GP) Ib/IX/V and GP IIb/IIIa receptors. In both forms of TTP, ULvWF polymers accumulate in the circulation, bind to both types of platelet vWF receptors under high-flow conditions, and cause the systemic platelet aggregation responsible for the arterial ischemic symptoms characteristic of the disorder.

Hemolytic-Uremic Syndrome

The great majority of cases of HUS are associated with a bloody diarrheal prodrome. The nondiarrhea-associated HUS, occurring predominately in adults, can be idiopathic, but in some instances has been found to be associated with HIV, bone marrow transplant, cancer and autoimmune diseases, or can be associated with cyclosporine, mitomycin, and other chemotherapeutic agents.

Pathophysiology

In the diarrhea-associated HUS, the causative agent has been identified as an *E. coli* which produces shiga-like toxins (verotoxins 1 and 2), the most common serotype being 0157:H7. *Shigella dysenteriae* is the other significant diarrhea-producing organism associated with HUS which produces shiga toxin.

Endothelial cells are the primary targets for shiga toxins (5, 34, 35). The verotoxins bind through their B subunits to the terminal trisaccharide linkage of globotriosyl ceramide (Gb3), the predominant membrane receptor for shiga toxin on the endothelial cell (5). The A subunit is then internalized by endocytosis and following proteolysis yields an enzyme capable of cleaving an N-glycoside bond resulting in removal of an adenosine nucleotide from the 28S ribosomal RNA that makes up 60S ribosomal subunits (5, 36, 37). This renders the ribosome inactive, suppressing protein synthesis leading to endothelial cell death. Gb3 expression is much greater in renal cells than in other cells, which probably accounts for the extensive renal disease occurring in HUS.

In both forms of HUS, it is thought, bacterial toxins cause endothelial cell toxicity and lead to organ damage. The endothelial cells become separated from the basement membrane and platelets are activated by contact with exposed collagen. Platelet aggregation occurs, aided by release of ULvWF multimers, which are also involved in HUS (38), reduced prostacyclin levels, which have anti-aggregating properties, and increased production of thromboxane, a platelet-aggregating agent produced by activated platelets (39, 40). Capillary and arteriolar lumina are narrowed by swollen endothelial cells, thrombi, and other vasoactive substances released by platelet and endothelial cells. These effects result in subsequent reduced kidney function (35).

Morigi et al. recently provided evidence supporting the role of verotoxin 1 (VT-1) in directly inducing platelet adhesion and thrombus formation on endothelial cells under high shear stress and showed that microvascular endothelial cells are significantly more sensitive to this thrombogenic effect of VT-1 than large vessel endothelial cells (41). In addition, they demonstrated the vital role of endothelial adhesion molecules in thrombus formation.

Treatment

Before the introduction of exchange plasmapheresis and infusion, TTP was fatal in 80% of cases. It is thought that plasma infusion replaces the metalloproteinase, while the exchange removes the autoantibody and possibly also the vWF polymers. Restoration of processing of ULvWF multimers was demonstrated in chronic relapsing TTP by infusion of fresh-frozen plasma (FFP) (42); cryosupernatant, which is the cryoprecipitate-depleted fraction of FFP that contains the metalloproteinase without the largest vWF polymers (42); or solvent/detergent-treated plasma which renders a potentially less infectious preparation (16). It has now been shown that these plasma preparations contain the vWF-cleaving protease (15, 23). If plasmapheresis is not immediately available, infusion of normal FFP can be used until plasmapheresis is arranged. Steroids have been shown to be effective (43), presumably in suppressing autoantibody production in acute TTP or TTP associated with ticlodipine.

Splenectomy was described by Cuttner in 1974 and has shown some success, especially in patients with frequent relapses, presumably because the spleen is a major site of autoantibody production (44). However, splenectomy can be very dangerous in these patients, given their profound thrombocytopenia and risk for severe hemorrhage.

Platelet transfusion should be avoided except for a life-threatening bleeding episode, since such treatment has been associated with worsening renal and neurologic status (45).

Suppressing autoantibody production with azathioprine or cyclophosphamide in patients with refractory, single episodes of TTP has shown some success (4, 46). There is some evidence that vincristine can also be helpful, as it depolymerizes platelet microtubules and may produce unfavorable vWF binding conditions by altering the GPIb-IX-V and/or GPIIb-IIIa receptors on platelet surfaces (47). Treatment options for TTP and HUS are summarized in Table 2.

Although the diarrhea-associated HUS is self-limited, patients with HUS require early and careful management of acute renal failure with fluid and electrolyte balance. Blood transfusions and hemodialysis are frequently required. In the adult form of HUS, FFP is recommended in addition, especially if the patient complains of neurologic symptoms. The use of FFP has been tried with variable success for HUS patients, although it remains unclear what its mechanism of action is.

TABLE 2
Treatment Options

TTP	
	Exchange plasmapheresis
	Cryosupernatant
	Glucocorticoids
	Splenectomy
	Immunosuppression
	Vincristine
HUS	
	Management of acute renal failure
	Blood transfusion
	Plasmapheresis

TABLE 3
Differentiating TTP and HUS

Similarities
- Clinical symptoms
- Labs (thrombocytopenia/hemolytic anemia/renal dysfunction)
- Endothelial cell damage/vWF multimer release/platelet thrombi

Differences
- Protease deficiency/inhibitor in TTP vs normal protease levels in HUS

Differentiating Between TTP and HUS

TTP and HUS are two entities with similarities in clinical symptoms and laboratory results, and in the fundamental mechanism of endothelial cell damage/loss of antithrombotic properties/resulting platelet thrombi formation, making it difficult to differentiate between them.

Although the precise mechanism by which each entity results in these thrombi remains somewhat elusive, evidence points toward involvement of ULvWF multimers in the pathogenesis of both TTP and HUS. TTP appears to involve defective von Willebrand factor-cleaving protease activity secondary to either an autoimmunity or deficiency, while HUS has been shown to have normal protease activity. Thus, further investigation of the predictive value of protease level measurement, which may enable physicians to distinguish between TTP and HUS, is warranted.

The finding of the protease difference may explain why plasma exchange therapy is more effective in TTP than in HUS. However, plasma exchange is not always effective in patients with an initial acute episode of TTP, possibly because more inhibitor is produced for a longer time, in which case more efficient techniques to remove autoantibody may increase survival. The important question is: Are TTP and nondiarrhea-associated HUS manifestations of one disease, representing different points along the same clinical spectrum, or are they indeed two distinct entities? (See Table 3.)

Future Therapies

It has been suggested that blockade of platelet receptors GPIb and GPIIb/IIIa (48–50) may be part of the future therapy of these entities, as binding to both receptors is required for initiation of the platelet-aggregating process. At present, two monoclonal antibodies which can block vWF binding to GIIb/IIIA are abciximab, which is used in angioplasty, and integrilin, which is a polypeptide derivative. These blockers may offer a therapeutic alternative for those patients with acute TTP who do not respond to FFP. However, these antibodies pose a potentially serious danger in that the patients who do not respond to plasma or steroids are generally extremely thrombocytopenic. Thus, using an agent which reduces the function of the few remaining platelets may cause fatal hemorrhage. These agents have thus far not been used in the treatment of TTP or HUS.

Currently, studies to develop an agent that can block the binding of large vWF multimers to platelet GPIb receptor are underway (48, 51). Hemorrhage is a complication of these compounds in severely thrombocytopenic patients and therefore initial clinical trials will have to be limited to patients with refractory TTP unresponsive to standard therapy.

Synthesis of the metalloproteinase for replacement may be another therapeutic option for patients with recurrent TTP. And finally, inhibitors of apoptosis may also play a therapeutic role in the treatment of TTP and HUS.

Summary

In summary, an increased awareness of characteristic symptoms and early diagnosis of TTP and HUS are of utmost importance, given the excellent results obtained with prompt plasma exchange therapy. Before the introduction of plasma exchange, the prognosis for these disorders was extremely poor, whereas now survival reaches upwards of 90%. However, the diagnoses of TTP and HUS often remain questionable, forcing the clinician to make the difficult decision of initiating plasma exchange therapy based on symptomatology and clinical judgment, and sometimes instinct. Frequently, it is possible to confirm the diagnosis only after initiating plasma exchange and seeing improvement in the patient's status. The quality of supportive measures has also contributed to the great difference in clinical outcome. However, since the acceptance of plasma therapy as the main treatment modality, there have been no further significant advances in the clinical management of TTP and HUS.

Because of the low incidence of these diseases, it has been difficult to perform prospective randomized trials of different treatment regimens. Thus, recommendations are based on reports of a limited number of patients, and anecdotal reports. It remains unclear how long plasma exchange therapy should continue. There are also no clear data on supportive measures most likely to be beneficial.

Tremendous progress has been made toward understanding TTP and HUS since TTP was first described at Mount Sinai more than 75 years ago. However, several questions remain. Are TTP and nondiarrhea-associated HUS actually the same disease entity? Can vWF-cleaving protease activity measurement predict which patients will benefit most from plasma exchange? What initiates apoptosis of endothelial cells in TTP, and are there other mechanisms of endothelial cell damage, for example, microbial infections? What is the precise sequence of events leading from endothelial cell damage to thrombotic microvessel obstruction in both TTP and HUS? What is the long-term outcome of patients after recovery from an episode of TTP or HUS, and what is the risk of relapse? Further efforts in understanding the pathophysiology, and investigating novel therapeutic options by way of future clinical trials will help shed more light on these two elusive disease entities.

References

1. Moschcowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries. Arch Intern Med 1925; 36(1):89–93. [Reprinted in this issue.]
2. Gasser C, Gautier E, Steck A, et al. Hämolytisch-urämische Syndrome: bilaterale Nierenrindennekrosen bei akuten erworbenen hämolytischen Anämien [German]. Schweiz Med Wochenschr 1955; 85:905–909.
3. Moake JL. Chow TW. Thrombotic thrombocytopenic purpura: understanding a disease no longer rare. Am J Med Sci 1998; 316(2):105–119.
4. Byrnes JJ, Moake JL. Thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome: evolving concepts of pathogenesis and therapy. Clin Haematol 1986; 15:413–442.
5. Moake JL. Haemolytic uraemic syndrome: basic science. Lancet 1994:343:393–397.
6. Mitra D, Jaffe EA, Weksler B, et al. Thrombotic thrombocytopenic purpura and sporadic hemolytic-uremic syndrome plasmas induce apoptosis in restricted lineages of human microvascular endothelial cells. Blood 1997; 89:1224–1234.
7. Dang CT, Magid MS, Weksler B, et al. Enhanced endothelial cell apoptosis in splenic tissues of patients with thrombotic thrombocytopenic purpura. Blood 1999; 93:1264–1270.
8. Asada Y, Sumiyoshi A, Hayashi T, et al. Immunohistochemistry of vascular lesions in thrombotic thrombocytopenic purpura, with special reference to factor VIII related antigen. Thromb Res 1985; 38:469–479.
9. Li JZ, Liu JW, Benito G, et al. Electron microscopic study of platelet agglutination induced by thrombotic thrombocytopenic plasma containing 37-Kda platelet agglutinating protein. Thromb Res 1989; 55:757–766.
10. Lian EC, Savaraj N. Effects of platelet inhibitors on the platelet aggregation induced by plasma from patients with thrombotic thrombocytopenic purpura. Blood 1981; 58:354–359.
11. Murphy WG, Moore JC, Barr RD, et al. Relationship between platelet aggregating factor and von Willebrand factor in thrombotic thrombocytopenic purpura. Br J Haematol 1987; 66:509–513.
12. Consonni R, Falanga A, Barbui T. Further characterization of platelet-aggregating cysteine protease activity in thrombotic thrombocytopenic purpura. Br J Haematol 1994; 87:321–324.
13. Wagner DD, Ginsberg D. Structure, biology, and genetics of von Willebrand factor. In: Hoffman R, Banz EJ Jr., Shattil SJ, et al., editors. Hematology: basic principles and practice. 2nd ed. New York: Churchill Livingstone; 1995. pp. 1717–1725.
14. Moake JL, Rudy C, Troll J, et al. Unusually large plasma VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med 1982; 307:1432.
15. Furlan M, Robles R, Galbusera M, et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 1998; 339:1578–1584.
16. Moake J. Chintagumpala M, Turner N, et al. Solvent/detergent treated plasma suppresses shear-induced platelet aggregation and prevents episodes of thrombotic thrombocytopenic purpura. Blood 1994; 84:490–497.
17. Frangos JA, Moake JL, Nolasco L, et al. Cryosupernatant regulates accumulation of unusually large vWF multimers from endothelial cells. Am J Physiol 1989; 256(6 Pt 2):H1635–H1644.
18. Tsai HM. Physiologic cleavage of von Willebrand factor by a plasma protease is dependent on its conformation and requires calcium ion. Blood 1996; 87:4235–4244
19. Furlan M, Robles R, Lamie B. Partial purification and characterization of a protease from human plasma cleaving von Willebrand factor to fragments produced by in vivo proteolysis. Blood 1996; 87:4223–4234.
20. Tsai HM, Sussman I, Nagel RL. Shear stress enhances the proteolysis of von Willebrand factor in normal plasma. Blood 1994; 83:2171–2179.
21. Stathakis P, Fitzgerald M, Matthias LJ. Generation of angiostatin by reduction and proteolysis of plasmin. Catalysis by a plasmin reductase secreted by cultured cells. J Biol Chem 1997; 272:20641–20645.
22. Furlan M, Robles R, Solenthaler M, et al. Deficient activity of von Willebrand factor-cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. Blood 1997; 89:3097–3103.

23. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998; 339:1585–1594.

24. Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. Blood 2001; 98(6):1662–1666.

25. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic throbocytopenia purpura. Nature 2001; 413(6855):488–494.

26. Neame PB. Immunologic and other factors in thrombotic thrombocytopenic purpura. Semin Thromb Hemost 1980; 6:416–429.

27. Joseph G, Smith KJ, Hadley TJ, et al. HLA-DR53 protects against thrombotic thrombocytopenic purpura/adult hemolytic uremic syndrome. Am J Hematol 1994; 47:189–193.

28. Tandon NN, Rock G, Jamieson GA. Anti-CD36 antibodies in thrombotic thrombocytopenic purpura. Br J Haematol 1994; 88:816–825.

29. Tsai HM, Rice L, Sarode R, et al. Antibody inhibitors to von Willebrand factor metalloproteinase and increased binding of von Willebrand factor to platelets in ticlopidine-associated thrombotic thrombocytopenic purpura. Ann Intern Med 2000; 132:794–799.

30. Moore JC, Hayward CP, Warkentin TE, Kelton JG. Decreased vWF protease activity associated with thrombocytopenic disorders. Blood 2001; 98:1842–1846.

31. Moake JL, Turner NA, Stathopoulos NA, et al. Involvement of large plasma von Willebrand factor (vWF) multimers and unusually large vWF forms derived from endothelial cells in shear stress-induced platelet aggregation. J Clin Invest 1986; 78:1456–1461.

32. Chow TW, Turner NA, Chintagumpala M, et al. Increased von Willebrand factor binding to platelets in single episode and recurrent types of thrombotic thrombocytopenic purpura. Am J Hematol 1998; 57:293–302.

33. Moake JL. Thrombotic thrombocytopenic purpura today. Hosp Practice (Off Ed) 1999; 34:53–59.

34. Levin M, Walters MD, Barratt TM. Hemolytic uremic syndrome. Adv Pediatr Infect Dis 1989; 4:51–81.

35. Kaplan BS, Cleary TG, Obrig TG. Recent advances in understanding the pathogenesis of the hemolytic uremic syndromes. Paediatr Nephrol 1990; 4:276–283.

36. Remuzzi G, Ruggenenti P. The hemolytic uremic syndrome. Kidney Int 1995; 47:2–19.

37. Obrig TG. Pathogenesis of shiga toxin induced endothelial cell injury. In: Kaplan BS, Trompeter RS, Moake JL, editors. Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. New York: Marcel Dekker; 1992. pp. 405–419.

38. Moake JL, Byrnes JJ, Troll JH, et al. Abnormal VIII: von Willebrand factor patterns in the plasma of patients with the hemolytic-uremic syndrome. Blood 1984; 64:592–598.

39. Brain MC. The haemolytic-uremic syndrome. Semin Hematol 1969; 6:162–180.

40. Goldstein MH, Churg J, Strauss L, Gribetz D. Hemolytic uremic syndrome. Nephron 1979; 23:263–272.

41. Morigi M, Galbusera M, Binda E, et al. Verotoxin-1 induced upregulation of adhesive molecules renders microvascular endothelial cells thrombogenic at high shear stress. Blood 2001; 98:1828–1835.

42. Moake JL, Byrnes JJ, Troll JH, et al. Effects of fresh-frozen plasma and its cryosupernatant fraction on von Willebrand factor multimeric forms in chronic relapsing thrombotic thrombocytopenic purpura. Blood 1985; 65:1232–1236.

43. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. N Engl J Med 1991; 325:398–402.

44. Cuttner J. Splenectomy, steroids, and dextran 70 in thrombotic thrombocytopenic purpura. JAMA 1974; 227:397–402.

45. Harkness DR, Byrnes JJ, Lian EC, et al. Hazard of platelet transfusion in thrombotic thrombocytopenic purpura. JAMA 1981; 246:1931–1933.

46. Moake JL, Rudy CK, Troll JH, et al. Therapy of chronic relapsing thrombotic thrombocytopenic purpura with prednisone and azathioprine. Am J Hematol 1985; 20:73–79.

47. Gutterman LA, Stevenson TD. Treatment of thrombotic thrombocytopenic purpura with vincristine. JAMA 1982; 247:1433–1436.

48. Sugimoto M, Ricca G, Hrinda ME, et al. Functional modulation of the isolated glycoprotein Ib binding domain of von Willebrand factor expressed in Escherichia coli. Biochemistry 1991; 30(21):5202–5209.

49. Turner NA, Moake JL, Kamat SG, et al. Comparative real-time effects on platelet adhesion and aggregation under flowing conditions of in vivo aspirin, heparin, and monoclonal antibody fragment against glycoprotein IIb-IIIa. Circulation 1995; 91(5):1354–1362.

50. Kamat SG, Turner NA, Konstantopoulos K, et al. Effects of integrelin on platelet function in flow models of arterial thrombosis. J Cardiovasc Pharmacol 1997; 29(2):156–163.

51. Yao SK, Ober JC, Garfinkel LI, et al. Blockade of platelet membrane glycoprotein Ib receptors delays intracoronary thrombogenesis, enhances thrombolysis, and delays coronary artery reocclusion in dogs. Circulation 1994; 89(6):2822–2828.

EDITOR'S NOTE

Classics in Medicine

Dr. Eli Moschcowitz

The Journal IS REPUBLISHING, with permission, the article by Dr. Eli Moschcowitz which follows this note. It originally appeared 78 years ago when he was an attending physician at The Mount Sinai Hospital. Dr. Moschcowitz was short in stature but had a giant intellect. He was an astute clinician well trained in pathology. This combination of talent and training made it possible for him to recognize a serious disease which had not yet been described. His original observations inspired many other clinicians and researchers to study this disease, as testified by many subsequent reports. New observations and expanded laboratory techniques resulted in an explosion of knowledge which led to a better understanding of the etiology and pathogenesis of this disease nearly eight decades later.

Reading Dr. Moschcowitz's article in its original version enhances the stature of the clinician's input in defining and describing illnesses. It is not often that a singular contribution can be identified. Thus, the original report by Dr. Moschcowitz serves as an ideal companion piece to the article by Drs. Shah and Rand which immediately precedes this editorial note. I can think of no better way for the reader to appreciate how much has been learned about this disease since Dr. Moschcowitz's initial report.

An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries:

An Undescribed Disease*

Eli Moschcowitz, M.D.
New York

This case is remarkable, clinically and anatomically.

Report of Case

History. K. Z., a girl, aged 16 years, was an elementary school graduate, had gone to business school, and had been employed for eight months preceding the illness. There were three other children, two younger and one older; all apparently were perfectly normal. There were no home difficulties, and poverty was not extreme. She had spent September 4 and 5 at Rockaway Beach, where she appeared in perfect health and spirits. She had returned home on the evening of September 5 and slept well. On the morning of September 6, she complained of weakness in the upper extremities and had pain on moving the wrists and elbows; she already had marked pallor and was slightly constipated. The symptoms increased in severity until she was admitted to the Beth Israel Hospital, September 15. While at home, she had a constant fever, the temperature rising once to 104 F. and staying at other times between 101 and 102 F.

Physical Examination. The patient was a pale girl with "café au lait" tinge. A few petechiae were present on the left arm. The lungs and heart revealed nothing abnormal. The spleen and liver were not enlarged. The abdomen was lax and not tender. September 18, the red blood count was 1,330,000; the hemoglobin, 40 per cent; the leukocytes, 12,600, of which 65 per cent were polymorphonuclears. The red cells revealed a central pallor, but there were no nucleated elements. A fragility test showed hemolysis to begin at 0.8, and to be complete at 0.19 (?). No platelet count was made. September 19, the red blood count was 1,120,000; the hemoglobin was 40 per cent, and the leukocytes were 19,000. A blood culture remained sterile.

The urine showed marked traces of albumin with hyaline and granular casts.

The blood chemistry, September 16, showed: urea, 21.2 mg. per hundred cubic centimeters; nonprotein nitrogen, 31.25 mg. per hundred cubic centimeters, and creatinin, 1.1 mg. per hundred cubic centimeters. The feces and gastric contents gave a marked reaction for occult blood.

Roentgen-ray examination of the chest showed nothing abnormal. The electrocardiogram showed inversion of the T wave in Lead III. The temperature, on admission, was 101.8 F. During the week the patient was in the hospital, it ranged between 100 and 102 F. The pulse varied between 100 and 130. The respiration was around 20. The systolic blood pressure was 130, and the diastolic, 60.

September 19, there was partial paresis of the left arm and leg; also, a slight facial paralysis. The following day, a double Kernig reflex was noted. That night there was pulmonary edema, which responded to treatment. Soon after, the patient went into coma; respirations became irregular, and she died, September 20. Dr. E. Libman, who saw this patient in consultation, recognized the condition as a new disease.

Necropsy. A partial necropsy was done. The body was pale and poorly nourished. The lower lobes of both lungs showed marked congestion. The heart was slightly enlarged; the left ventri-

---

Reprinted with permission from Archives of Internal Medicine 1925; 36(1):89–93. Copyrighted 1925, American Medical Association.

* Read before the New York Pathological Society, Feb. 7, 1924.

cle was hypertrophied; the muscle was firm and pale. The mitral and aortic valves were normal. The liver was slightly enlarged, pale and fatty; there was slight nutmeg change. The spleen measured 11 by 8 by 3 cm., and weighed 165 gm. The surface was smooth. On section, the organ was deep mahogany red, somewhat soft and velvety. The malpighian bodies were prominent. The kidneys were large; the capsules were smooth and not adherent; on section, the organ was deep red.

The anatomical diagnosis was anemia; acute congestion at the bases of both lungs; hypertrophy of the left ventricle of the heart; hyperplasia of the spleen, and congestion of the liver and the kidneys.

Microscopic Examination. The lungs were edematous; at the bases, there was congestion of the parenchyma. The heart muscle revealed a striking appearance. With the low power of the microscope, practically every field revealed from one to a dozen structures that were unquestionably thrombi in the terminal arterioles or capillaries. These varied in appearance and revealed progressive changes depending on the amount of organization that had taken place. The earliest (Fig. 1) showed merely a plugging of the vessel with a hyaline mass which either partially or completely filled the lumen. Usually, even in this stage, the plug, if not in intimate contact with the wall of the vessel, was surrounded by a layer of flat cells of the fibroblastic type which was distinct from the endothelial intima. In older plugs (Figs. 2 and 3), fibroblasts penetrated into the hyaline mass, and the older the plug, the greater became the amount of fibroblastic infiltration at the expense of the hyaline material; eventually, a small fibroblastic tubercle-like structure was formed. In some of these thrombi, the origin of these fibroblasts from the endothelium of the vessel was plainly discernible. At the same time, the process of organization within the lumen was accompanied by a fibroblastic process around the wall of the vessel in concentric fashion; with the van Gieson stain, some gave the reaction for fibrous tissue. Karyokinetic figures in these fibroblasts were common. In some vessels in which the plug had not completely filled the lumen, tiny spaces were formed in which fresh red cells were visible Only the terminal arterioles and capillaries were involved. The larger vessels with well defined muscular walls showed no change whatever, either in the form of thrombosis or changes in the intima. Every section of heart muscle was involved, the ventricles, the auricles, the papillary muscles and the septum; they were even visible in some of the vessels of the precordial fat. In addition, there was moderate edema of the parenchyma. The liver showed a

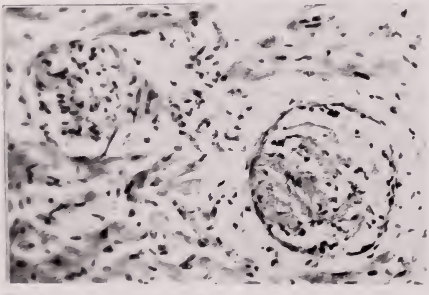
Fig. 1. Section of heart muscle, showing hyaline thrombi in early stage.

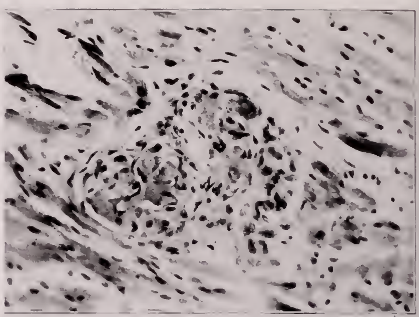
Fig. 2. (Top) Section of heart muscle, showing hyaline thrombi with beginning organization.

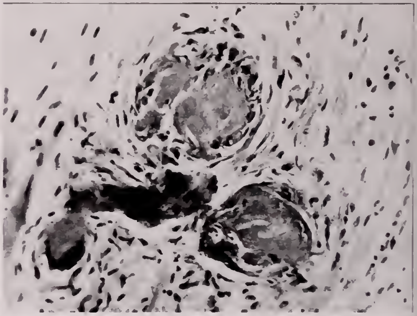
Fig. 3. (Bottom) Section of heart muscle, showing hyaline thrombi with beginning organization.

moderate fatty infiltration and slight congestion around the central veins. Very few hyaline thrombi in the early stages were noted. The spleen showed enormous congestion of the sinuses. A few hyaline thrombi were present in some of the central vessels of the malpighian bodies. The kidneys showed marked parenchymatous degeneration in the tubules and congestion of the parenchyma. The malpighian tufts were clear. Many of the arterioles and capillaries in the middle zone, in the region of the vasa recta, showed hyaline thrombi of the same morphology as those in the heart (Fig. 4). No bacteria, tubercle bacilli or spironema pallida were found in any of the tissues.

A fairly complete search of the medical literature fails to reveal a case resembling this, either clinically or anatomically. Hyaline thrombi have long been recognized but never in respect to the enormous spread and distribution revealed in this case. Klebs (1) apparently was the first to describe these thrombi; he noted them in cases of extensive burns. They have been described in a wide variety of conditions. Thus, Kaufman (2) found capillary red cell thrombi in cases of mercury poisoning. Schmorl (3) found them in the stomach and liver after abrin poisoning. Flexner (4) noted such thrombi in the neighborhood of ulcerated typhoid ulcers of the ileum and in the lung, associated with bronchiectasis; also in the liver in eclampsia, and in the stomach after carbolic acid poisoning. He also states that they have been found in pneumonia, diphtheria and in some of the acute infectious diseases. Loeb, Stricker and Tuttle (5) noted red cell thrombi in the lungs of animals after the injection of a foreign serum. Dietreich (6) found such thrombi in animals after the injection of an extract from beans. Bacterial infections are common causes of such thrombi, for they have been produced experimentally, in infections, by the hog cholera bacillus (Boxmeyer [7]), the pneumococcus and the staphylococcus aureus.

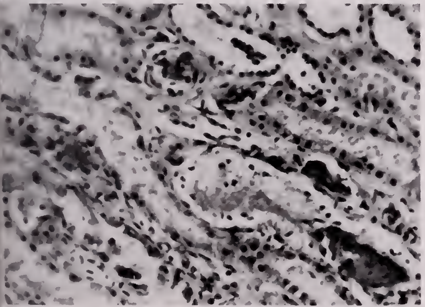

Fig. 4. Section of kidney, showing hyaline thrombi in terminal arterioles.

The true pathogenesis of hyaline thrombi was not known until Flexner showed that they arose from agglutinated red cells. This he proved by injecting the highly agglutinative substance, ricin, into rabbits. He concludes that when red cell thrombi are old or when agglutination is compact, they have the appearance of hyaline thrombi. He also states that poisons that destroy red blood corpuscles rapidly provoke agglutinative thrombi, and that the so-called fibrin ferment thrombi are probably agglutinative thrombi. Pearce (8), indeed, obtained hyaline thrombi in the liver associated with focal necroses by injecting agglutinating serums. He also injected filtered autolyzed products of various bacteria which possess hemagglutinins of low activity and obtained similar necroses of the liver associated with fused red blood cell thrombi, i.e., structures resembling hyaline thrombi.

In this condition, it is interesting to note that, as far back as 1875, Landois (9) found that an injection of foreign blood causes multiple capillary thrombosis.

I have learned that Dr. Max Lederer of Brooklyn has seen four cases clinically identical with the one described in this report. He permits me to state that, thus far, no cause has been found, and all four patients recovered promptly after a single transfusion of blood.

From these observations we conclude that death, in the case described, resulted from some powerful poison which had both agglutinative and hemolytic properties. If opportunity offers, further investigation will be made of this strange disease with strange pathologic morphology.

References

1. Klebs: Handb. d. path. Anat. Berlin, 2:114, 1868–1880.
2. Kaufman, quoted by Dietreich [Reference no. 6].
3. Schmorl: Jahresb. d. Gesellsch. f. Nat.-u. Heilk. in Dresd., 1899–1900, quoted by Flexner [Reference no. 4].
4. Flexner: J. M. Res. 8:316, 1902.
5. Loeb, Stricker and Tuttle: Virchows Arch. f. path. Anat. 201:5, 1910.
6. Dietreich: Centralbl. f. Path. 23:372, 1912.
7. Boxmeyer: J. M. Res. 9:146, 1903.
8. Pearce and Winne: Am. J. M. Sc. 128:669, 1904.
9. Landois: Die Transfusion des Blutes, Leipzig, 1875, p. 225.

INFORMATION FOR AUTHORS

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of The Mount Sinai Hospital*, is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and other major databases. The abstract and full text of each published article is posted on *The Journal's* web site <www.mssm.edu/msjournal> where it can be accessed by the reader. *The Journal*'s web site is linked to that of the National Library of Medicine. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcomed.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@mssm.edu; world wide web: www.mssm.edu/msjournal.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and either (3) the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in *The Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal*'s office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations and a disk (see below). **Manuscripts must be computer generated, double spaced throughout (including references, legends, and tables)**, on one side of $8^1/_2 \times 11$ inch white bond paper with **one inch** margins. The title page must be entirely separate and should designate the location(s) where the work was done, and the name and address of the corresponding author. The abstract page(s) should be numbered sequentially as i, ii, iii, etc. A separate page should be used for each table. The legends, in numerical sequence, should be typed together on one or more pages (if needed). A separate page, or pages, should list the references in the sequential order they are cited for the first time in the narrative text. A disk should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted (Windows, MAC), and the software used (WordPerfect, MS Word, etc.). PC format is preferred, but a high-density, formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or WordPerfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page(s) or in legends. Define all abbreviations on first use in the body of the manuscript. All abbreviations used in a table must be defined at the bottom of the table.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher, giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If the manuscript deals with specific patients for whom identifiers (as defined by HIPAA) are provided, the consent of each patient for the release of information must accompany submission of the manuscript. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office (or its equivalent) which supervises such work.

Title Page. This page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, and middle initial(s), if any, and not more than two academic degrees; (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and telephone and FAX numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom an offprint is to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and (9) **a running head of fewer than 40 letter spaces.** At the bottom of the title page, **list 3 to 10 key words or phrases** to facilitate computer searches in accord with medical subject headings from *Index Medicus*. If more than one sheet is needed, label the supplemental sheet as "Title Page (cont.)."

Abstract. All articles must include an abstract of not more than 400 words. The pages containing the abstract should be numbered sequentially as i, ii, iii, etc. This abstract will be published in *The Journal* with the article. Enough detail should be provided in the abstract so that it will be sufficiently informative to stand alone when placed on *The Journal*'s web page (prior to publication of the entire article in *The Journal*). Abstracts should be double spaced. Abstracts for manuscripts specifically describing original clinical and/or laboratory research should be structured in four paragraphs:

Background: what problem(s) was (were) addressed;
Methods: how the study was performed;
Results: the most significant results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page and also after the abstract to facilitate computer searches. **Repeat at the end of the abstract the same key words which are listed on the title page.**

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning, in conformity with the style used by *The Journal*. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp.

high-contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in. width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of 3¹/₈ inches. **The type of stain and power of magnification (e.g., 10X, 40X, 100X, etc.) must be indicated in the relevant legend**. Electron photomicrographs should have internal scale markers. On the back of each print and photograph, affix a gum label on which the number of the figure has been written to correspond to its identification in the text, as well as the title of the manuscript, first author's last name, and the word "top" and an arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial features should be masked to prevent identification of the subject unless they include details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

The Journal does not publish color images unless the author is willing to pay for the additional expense involved. Should the author wish to consider publishing images in color, 3 copies of each color print must be included with the manuscript. If the manuscript is accepted, the author will be informed of the extra cost involved. A check for this amount must be received prior to publication. If, however, the author wishes to have color images appear **only in *The Journal's* web page version** of the article, one copy of each color print (rather than 3) along with the 3 black and white glossy prints must be submitted with the manuscript. The web page version of the manuscript will not involve additional expense to the author.

Legends. Legends should not duplicate the text. They should appear together in numerical order, typed double spaced, on one or more pages following the text. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle," etc.) or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Footnotes. Except as noted above in the section "Units of Measurement," the use of footnotes is to be avoided. All relevant information should be incorporated directly into the narrative text, and appropriately cited as noted below in the section "References."

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (**TABLE 1**, etc., in bold type) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text, and type the title, *in italics*, on a separate line below the table's number. Identify all abbreviations and/or symbols used in the table in a footnote at the bottom of the table.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., **Cytomegalovirus (1), steroids (2, 3), and recreational drugs (4-6) have all been implicated (7).** Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus*. The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled "References" are illustrated in the version of "Uniform Requirements" published in *The New England Journal of Medicine* referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style shown in the examples below. The list of references should not be formatted as "Endnotes."

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309–315.

3. Couser WG. Glomerular diseases. In: Stein J, editor. Internal medicine. 2nd ed. Boston: Little Brown; 1987. pp. 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then "et al."

A citation to an article that has not been published in print (journal, book) and that has been obtained by accessing a website must include, in addition to the names of the authors and the title of the article, the precise uniform resource locator (URL) address at which the article can be found and accessed. This address can usually be found as a long stream of characters and numbers after the prefix "http://www..........."

References to unpublished data (unless the information is in press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission.

If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.

Proofs. A revised, copy-edited manuscript will be sent to the corresponding author as soon as it is available, for necessary corrections only. **Stylistic changes should not be made**. All corrections should be made on this copy, which must be returned to the *Journal* office as soon as possible (see "Communications" above). This corrected, revised, edited version of the manuscript will be sent to the printer for typesetting directly from a disk. "Galleys" will not be sent to the corresponding author for review.

Offprint Orders. A "Request for Offprints" form will be sent to the corresponding author. If offprints are desired, the form must be returned to the editorial office. When the article is scheduled for publication, an "Offprint Order Form" and "Shipping Label" will be sent to the corresponding author. These must be completed and returned with a check for the exact amount in US dollars made out to *The Mount Sinai Journal of Medicine*. Please indicate on the check the last name of the first author, and the title of the article. If, for one reason or another, an "Offprint Order Form" and "Shipping Label" are not received by the corresponding author, they may be obtained directly from the *Journal* office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the total number of printed pages and whether covers are desired. The cost of delivery must be added to the cost of the offprints. Information on cost of other than routine delivery can be obtained from the *Journal* office.

09/2003

3 4805 0795225 8

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Forthcoming: Grand Rounds

A Review of Heart Failure Treatment
Gordon H. Guyatt and P.J. Devereaux
McMaster University
Hamilton, Ontario, Canada

Renal Artery Disease: Diagnosis and Management
Jeffrey W. Olin
Mount Sinai School of Medicine

The Multidisciplinary Approach to Hemodialysis Vascular Access at The Mount Sinai Hospital
Joseph A. Vassalotti, Abigail Falk,
Victoria Teodorescu,
and Jaime Uribarre
Mount Sinai School of Medicine

Theme Issues

Ethics 2001 — Medicine, Money and Morals
Rosamond Rhodes and Daniel A. Moros, Editors

Minimally Invasive Vascular Surgery: The Evolution of Endovascular Therap
Michael L. Marin, Harold A. Mitty, Larry H. Hollier, and Valentin Fuster, Edito

Available now:

Methadone Symposium – Part 1:2000
Volume 67: Numbers 5 & 6. 125 pages, $40.00

Methadone Symposium – Part 2:2001
Volume 68: Number 1. 78 pages, $25.00

Issues in Medical Ethics — Understandin
Professionalism and Its Implications for
Medical Education
Volume 69: Number 6. 71 pages, $25.00

Visit our web page — http://www.mssm.edu/msjournal

THE MOUNT SINAI JOURNAL OF MEDICINE

OLUME 70 NUMBER 6 NOVEMBER 2003

MINIMALLY INVASIVE VASCULAR SURGERY:

THE EVOLUTION OF ENDOVASCULAR THERAPY

Michael L. Marin, Harold A. Mitty, Larry H. Hollier, and Valentin Fuster, Guest Editors

PART 1

CONTENTS

ntroduction *Michael L. Marin, Harold A. Mitty, Larry H. Hollier and Valentin Fuster* 357

Advances in Angiography and Their Impact on Endovascular Therapy *Harold A. Mitty* 359

Duplex Ultrasonography and Its Impact on Providing Endograft Surveillance *Victoria J. Teodorescu, Nicholas J. Morrissey, and Jeffrey W. Olin* 364

mpact of CT Angiography on Endovascular Therapy *Robert A. Lookstein* 367

New Techniques and Applications for Magnetic Resonance Angiography *Jeffrey P. Goldman* 375

Devices and Techniques for Endovascular Surgery: Catheters, Stents, Coated Stents, and Stented Grafts *Lev Pukin* 386

Endovascular Therapy for Atherosclerotic Occlusion and Stenosis from the Infrarenal Aorta to the Infrapopliteal Arteries *F. Scott Nowakowski and Hank J. Freeman* 393

Revascularization of Aortic Arch Branches and Visceral Arteries Using Minimally Invasive Endovascular Techniques *Shyamkumar N. Keshava and Abigail Falk* 401

Endovascular Repair of Diffuse Atherosclerotic Occlusive Disease Using Stented Grafts *Edwin C. Gravereaux and Michael L. Marin* 410

Drug-Eluting Stents in Peripheral Vascular Disease: Eliminating Restenosis *Sharif H. Ellozy and Alfio Carroccio* 417

Endovascular Treatment of Abdominal Aortic Aneurysms *Peter L. Faries, Nicholas J. Morrissey, Victoria J. Teodorescu, Larry H. Hollier and Michael L. Marin* 420

List of Journal Reviewers in 2003 427

Author, Subject, Title Index to Volume 70 428

Required Form for Authors C3

SAINT BARNABAS HEALTH CARE SYSTEM

LIBERTY HEALTHCARE SYSTEM, INC.

Veterans Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by the Mount Sinai Medical Center of New York and has following affiliates: Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY; Saint Barnabas Health Care System, Livingston, NJ; Newark Beth Israel Medical Center, Newark, NJ; Liberty HealthCare System, Inc., Jersey City, NJ.

Editor-in-Chief

Sherman Kupfer, M.D.

Associate Editors

Leslie A. Kuhn, M.D.
Philip S. Ledereich, M.D.

Administrative Assistant

Ron Stein

Assistant Editor for Housestaff

Leora Horwitz, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

Scott H. Barnett, M.D.
J. Hugh Baron, D.M.
David H. Bechhofer, Ph.D.
Constantin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Donald Brief, M.D.
Daniel Buchbinder, D.M.D. M.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., M.P.H., M.P.P.
William H. Constad, M.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Jack Hirschowitz, M.B., Ch.B.
Fred M. Jacobs, M.D., J.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M. Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkovitz, M.D.
Dana M. Lewis, M.L.S.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Myron Miller, M.D.
Richard Panush, M.D.
Barbara E. C. Paris, M.D.
Jerome G. Porush, M.D.
Georges R. Ramalanjaona, M.D., D.Sc.
Veronica A. Ravnikar, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Tibor Rohacs, M.D.
Gregory J. Rokosz, D.O., J.D.
Joshua Rosenblatt, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Harry Schanzer, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Janet B. Serle, M.D.
Phyllis Shaw, Ph.D.
Scott H. Sicherer, M.D.
Barry D. Stimmel, M.D.
Nelson N. Stone, M.D.
Max Sung, M.D.
Jules A. Titelbaum, M.D.
Thomas A. Ullman, M.D.
Richard P. Wedeen, M.D.
Klaudiusz R. Weiss, Ph.D.

Editorial Board

Barry S. Coller, M.D.
Kenneth L. Davis, M.D.
Panayotis G. Katsoyannis, Ph.D.
Jack G. Rabinowitz, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, Septe October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029- Subscription price: individuals (U.S. and Canada), $79 per year; libraries and institutions (U.S. and Canada), $121 per year; individuals (o U.S. and Canada), $105 per year; libraries and institutions (outside U.S. and Canada), $147 per year. The charge per copy of a single n issue is $25, for a two-number issue is $50. New subscriptions begin with the first issue of the calendar year. Send notice of change of a 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send a changes to *The Mount Sinai Journal of Medicine*, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212 6108. Fax (212) 722-6386. e-mail: msjournal@mssm.edu; web page: www.mssm.edu/msjournal. Copyright 2003.

DISCLAIMER: The statements and opinions expressed in *The Journal* by authors and contributors are solely their own and not those of The Moun Medical Center or *The Mount Sinai Journal of Medicine*. All advertisements are expected to conform to ethical standards, and their appearance does no endorsement or approval by The Mount Sinai Medical Center and/or *The Mount Sinai Journal of Medicine* of the products with respect to effectiveness, qu safety. The Mount Sinai Medical Center and *The Mount Sinai Journal of Medicine* do not hold themselves responsible for statements made by the aut contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisement

COPYRIGHT Material printed in *The Journal* is protected by copyright. In accord with U.S. Copyright law, no part of *The Journal* may be reproduced, displayed or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior w permission to do so. Permission should be requested from The Editor, *The Mount Sinai Journal of Medicine*, The Mount Sinai School of Medicine, Box 10 One East 100th Street, New York, NY 10029-6574.

Introduction

Minimally Invasive Vascular Surgery

Michael L. Marin, M.D.[1], Harold A. Mitty, M.D.[2], Larry H. Hollier, M.D.[1], and Valentin Fuster, M.D.[3]

Minimally invasive vascular surgery, or endovascular therapy, comprises a series of techniques which employ specialized tools to alter vascular pathology from the luminal surface of the vessel. These techniques include the ability to treat the affected, diseased artery from a remote, easily accessible peripheral vessel. The development of endovascular therapy has a rich history, which has been closely entwined with the development of diagnostic angiographic techniques.

Angiography of cadavers rapidly followed Roentgen's initial discovery of x-ray imaging of bones in 1895. The medical implementation of clinical diagnostic angiography was delayed because of the lack of a suitable non-toxic contrast agent. In 1927 this problem was partially resolved by Moniz, who was the first to use a 22% sodium iodide solution to image the cerebral circulation (1).

Moniz's concepts were rapidly expanded by Dos Santos and associates, who applied these techniques to the peripheral circulation, thus developing arteriography and aortography (2). Dos Santos' group was the first to clearly delineate atherosclerotic lesions, arterial aneurysms and patterns of arterial collateralization. The dramatic foundation of cardiac arteriography also occurred during this time period with the work of Werner Forssmann, who was then a surgical intern in Berlin. Defying his superiors, who refused to allow him to conduct cardiac catheterization experiments, he catheterized himself in 1929, advancing a urethral catheter from his basilar vein into his right ventricle under fluoroscopic guidance. It was not until 1941, when Andre Cournand performed his important studies on cardiopulmonary physiology, that the true potential of cardiac catheterization became apparent (3). Cournand, Forssmann and D.W. Richards shared the Nobel Prize in Physiology and Medicine in 1956, for these important accomplishments.

Improvements in diagnostic arteriography evolved rapidly in the 1950's with the better access techniques of Seldinger (4), the coronary angiographic techniques of Sones (5), and the specialized guidewires of Amplatz (6). These improvements in diagnostic imaging techniques made possible the development and eventual implementation of therapeutic endovascular procedures.

One of the first minimally invasive catheter-based therapies to be introduced was by Fogarty, who used a balloon catheter to remotely extract intravascular thrombi (7). This approach to arterial embolectomy completely circumvented the need for standard extensive arterial revascularization procedures, which were associated at the time with significant morbidity and perioperative mortality. The application of catheter-based therapy to chronic atherosclerotic occlusive lesions of vessels was subsequently initiated by Dotter in 1964, with the percutaneous insertion of Teflon catheters over a guidewire to "dilate" a stenotic lesion (8). Technical modification of Dotter's technique by Grüntzig and others led to the development of the angioplasty balloons and their eventual application to coronary stenosis (9).

Improved therapeutic devices for endovascular therapy continue to be developed, while advances in diagnostic imaging occur. High resolution, digital subtraction arteriography, ad-

---

From the Departments of [1]Surgery, [2]Radiology, and [3]Cardiology, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Michael L. Marin, M.D., Henry Kaufmann Professor of Vascular Surgery, Chief, Division of Vascular Surgery, Box 1273, Mount Sinai School of Medicine, 1 East 100th Street, New York, NY 10029; E-mail: michael.marin@msnyuhealth.org

Key Words: Minimally invasive vascular surgery, vascular surgery, angiography, percutaneous angioplasty, catheterization.

vanced CT angiography, detailed duplex ultrasonic imaging, magnetic resonance angiography have all evolved to advance the limits of endovascular therapy. Data from these specialized techniques are already directing vascular therapy in new and exciting ways. The ability to characterize atherosclerotic plaque or analyze the integrity of the vascular wall are a few of the areas that are actually guiding treatments today (10). High resolution CT images combined with finite element analysis also holds the promise of aiding in the prediction of which aortic aneurysms are at immediate risk of rupture, mandating immediate repair (11). It is becoming increasingly clear that the fusion of imaging and therapeutic intervention will continue to assist us in providing the highest quality of care to the vascular disease patient. The history of this field is rich and continues to bear fruit of extraordinary value. This theme issue of *The Mount Sinai Journal of Medicine* explores the cutting edge of diagnostic and therapeutic endovascular therapy, setting the standard for the present and future care of patients with vascular disease.

References

1. Moniz E. Arterial encephalography: its importance in the location of cerebral tumors. Neurologique 1927; 48:72.
2. Dos Santos R. Arteriography of the limbs, with the collaboration of Augusto Lamas and J Pereira Caldas. Medicina Contemanea 1929. Reprinted in Viega-Pires J, Grainger R, editors: Pioneers in angiography: The Portuguese school of angiography. Boston, 1987. MTP Press.
3. Cournand A. Cardiac catheterization: development of the technique, its contributions to experimental medicine, and its initial applications in man. Acta Med Scand Suppl 1975; 579:3–32.
4. Seldinger S. Catheter replacement of the needle in percutaneous arteriography: a new technique. Acta Radiol 1953; 39:368–376.
5. Sones F, Shirle E. Cine coronary arteriography. Mod Con Cardiovasc Dis 1962; 31:735.
6. Rogers LF. Kurt Amplatz: a radiology giant steps aside. AJR Am J Roentgenol 1999; 173:521.
7. Fogarty T, Cranley J, Krause R, et al. A method for extraction of arterial emboli and thrombi. Surg Gynecol Obstet 1963; 116:241–244.
8. Dotter C, Judkins M. Transluminal treatment of arteriosclerotic obstruction: description of a new technic and a preliminary report of its application. Circulation 1964; 30:654–670.
9. Grüntzig A, Hopff H. Perkutane Rekanalisation chronischer arterieller Verschlusse mit einem neuen Dilatationskatheter: Modification der Dotter-Technik. Dtsch Med Wochenschr 1974; 99:2502–2510, 2511.
10 Choi CJ, Kramer CM. MR imaging of atherosclerotic plaque. Radiol Clin North Am 2002; 40(4):887–898.
11. Fillinger MF, Marra SP, Raghavan ML, Kennedy FE. Prediction of rupture risk in abdominal aortic aneurysm during observation: wall stress versus diameter. J Vasc Surg 2003; 37:724–732.

Advances in Angiography and Their Impact on Endovascular Therapy

HAROLD A. MITTY, M.D.

Abstract

Transvascular therapy has progressed rapidly due to improvements in imaging equipment and endovascular devices. Interventional fluoroscopic equipment and portable machines are able to produce high-resolution digital images in well-lighted procedure rooms.

Catheters and guidewires are now available in a variety of shapes, diameters and lengths, allowing entry into distal, small, and tortuous vessels. This in turn permits targeted local therapy of tumors and bleeding sites, as well as endovascular treatment of diseased vessels.

Key Words: Angiography, endovascular therapy.

IMPROVEMENTS IN IMAGING and endovascular diagnostic and therapeutic devices such as catheters, guidewires, balloons and stents have promoted the growth of endovascular and transvascular therapy.

Imaging in the Modern Interventional Suite

Basic Room Design

The design of dedicated interventional suites has progressed with the realization that these rooms will function as operating rooms. In fact, many procedures performed in interventional rooms in the radiology department may be more complex and potentially more dangerous than those performed in the traditional operating room. For this reason, interventional radiology rooms are constructed with adequate space for procedure tables, Mayo stands and other equipment. In addition, there must be adequate space for anesthesia staff and their equipment. These rooms are now designed with wall suction and appropriate gas lines. Many rooms are "OR compatible," meaning that the floors, ceiling and cabinets meet operating room specifications. In addition, the number of air exchanges per minute must meet local health code standards. Electrocardiography, pulse oximetry, and blood pressure monitoring may be done only in rooms where conscious sedation or anesthesia is administered.

Most major X-ray manufacturers have designed their rooms so that the gantry of the unit can be placed at the head of the table or on either side of the table. This assures easy access to either groin for femoral artery and/or vein puncture, as well as access to the neck for transjugular procedures. In addition, the TV monitors are usually placed on a movable track system, which allows them to be moved to either side of the table for viewing. Finally, many of the imaging controls are at tableside, allowing manipulations such as shutter control, image size adjustment, roadmapping and filming to be performed by the physician (1).

Fluoroscopy

The replacement of conventional fluoroscopy with image intensification coupled to a TV chain has permitted fluoroscopically guided procedures to be performed in a lighted room. This has added an element of comfort for the operator as well as increased safety for the patient. The use of image intensification has also decreased the amount of X-ray exposure necessary to produce an adequate real-time image. The dose of radiation to both the patient and operator also has been decreased with the advent of better collimation and pulsed fluoroscopy (2,

---

Address all correspondence to Harold A. Mitty, M.D., Professor of Radiology and Urology, Department of Radiology, Box 1234, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

3). This has become more important as procedures using fluoroscopic techniques have become longer. Nevertheless, it is important to keep track of total fluoroscopic time. Reports have appeared of radiation-induced skin burns related to long procedures such as transjugular intrahepatic porto-systemic shunting (TIPS), cardiac catheterization, etc. (4–6).

One cannot overemphasize the importance of high-quality fluoroscopic equipment that is coupled to TV chains in which the resolution of the monitors is 1,024 lines. This affords excellent resolution which allows visualization of very small catheters and guidewires as well as clear imaging of small vessels.

Roadmapping is a technique built into most new interventional imaging systems. This allows the operator to visualize the course of a catheter and/or wire through a previously opacified vessel, the image of which is stored and displayed on a TV monitor. This technique facilitates the catheterization of specific branches without the need for guidewire removal or repeated injections of contrast material to define catheter position.

Image Recording

Until recently, most angiography rooms were equipped with some sort of rapid film changer. To continue filming usually required moving the patient over the film changer, where a second-ceiling mounted X-ray tube was used to make the film exposures. This proved cumbersome, and catheters were often dislodged during movement of the patient. The problem was overcome by mounting the film changer next to the image intensifier in such a fashion that it could be moved into place without moving the patient. In such systems, the same X-ray tube is used for fluoroscopy and film exposure. These film changers are still available as an option for most interventional rooms. However, film changers are rarely used nowadays, because of the time and expense associated with conventional film processing and because of the availability now of digital imaging techniques.

The newer digital angiography equipment provides resolution that is quite acceptable for all vascular procedures. Thus, most new rooms have digital subtraction angiography as the standard means of recording vascular images. These rooms also have software that allows the images to be post-processed. Techniques such as pixel shifting allow misregistration artifacts to be eliminated. Subtraction can be done in real time or the bony background can be restored when indicated. Brightness and contrast controls allow image improvement to be controlled by the physician or technician. Finally, the images are stored and archived in a digital format, thus eliminating the problem of lost films.

Portable C-arm fluoroscopic units, which are now also available, allow most of these techniques to be employed in the operating room or at the bedside.

Ultrasound Guidance

Many interventional rooms have the available option of an integrated ultrasound unit. Some interventionalists use units which can be moved from room to room. These can be used to "find" vessels to puncture, particularly veins. The internal jugular vein is a common site for venous access procedures, inferior vena cava filter placement, and pulmonary arteriography. The complication of inadvertent carotid artery puncture and pneumothorax are all but eliminated when ultrasound guidance is used.

Small dedicated ultrasound units are also useful for performing percutaneous nephrostomy, abscess drainage, peritoneal catheter insertion and thoracentesis of loculated collections.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are increasingly useful in the management of patients with vascular disease (7).

Needles and Entry Systems

Needles

Vessels are usually punctured using "single-wall" or "double-wall" needles. The single-wall needle has no stylet, so that when the vessel is punctured, blood returns as the needle enters the lumen. Using it provides the advantage of avoiding the puncture of the posterior wall of the target vessel. However, it is not uncommon to traverse the vessel and not get blood return. This probably results from the anterior wall of the vessel collapsing against the posterior wall as the puncture is being performed. For this reason, it is important to withdraw a single-wall needle slowly, while looking for blood return. Using the single-wall needle also has the disadvantage of making guidewire exchange more difficult, since there is no stylet to replace while a new wire or one of different shape is obtained.

The "double-wall" or Seldinger needle has a stylet, which actually punctures the vessel. Once the stylet is removed, one is left with a blunt cannula tip in the vessel. The major disadvantage of using this needle is that there is a puncture in the posterior wall of the vessel, which may be a site for bleeding, particularly in patients with coagulation disorders or hypertension. However, one can perform a single-wall puncture with this needle in 20–30% of cases when the maximum pulsation of the vessel is transmitted to the hand holding the needle. A short thrust at this site will allow an anterior-wall-only puncture.

Micropuncture Sets

Micropuncture sets come as 4 or 5F systems. The vessel is punctured with a 21-gauge needle through which an 0.018 inch guidewire is advanced. The needle is removed and the micropuncture sheath is advanced over the wire into the vessel. The 0.018 inch wire and the inner sheath are removed, leaving the outer 4–5F sheath in place. An 0.035 inch wire is then advanced into the vessel, and this wire is used to complete the standard catheterization. By starting with a 21-gauge needle, the risk to the vessel or adjacent non-target structures is minimized.

Larger systems such as the 6F Neff set (Cook Inc., Bloomington, IN) and Accustik® (Boston Scientific, Watertown, MA) also allow the operator to progress from a 22–21 gauge needlestick to placement of these 6F sheaths. These are longer than the micropuncture sets and are adaptable to transhepatic hepatic vein, portal vein and biliary duct punctures. They are also widely used as access for abscess drainages and percutaneous nephrostomy. They may also be used for translumbar puncture of the aorta and vena cava. These 6F sheaths will accept 4F diagnostic catheters with various shapes, so that selection of branches may be performed without removing the sheath.

Catheters and Guidewires

Standard Diagnostic Catheters

A wide selection of diagnostic catheters is now available from many manufacturers. It is the responsibility of the angiographer/interventionalist to be familiar with the variety of shapes, sizes, lengths, coatings, and handling characteristics of available products. A particular catheter may be ideal for one situation and unsuitable for another. For example, a hydrophilic catheter may track better in a tortuous vessel, but may be too slippery in the operator's hands in another situation requiring application of high torque. While polyethylene-and-nylon-composite catheters work well as conduits for stainless steel embolization coils, these coils may become impacted in polyurethane catheters due to the high coefficient of friction of this material.

Radio-opacity of catheters is important, so that they can be visualized fluoroscopically. Manufacturers have increased radio-opacity of the catheter tips and distal curved portions, so that manipulations during fluoroscopy are more easily observed.

The diameters of diagnostic catheters have decreased as newer materials and manufacturing techniques have evolved. Standard diagnostic catheters are now in the 4–5F range. The small size of these catheters is associated with a lower rate of complications at the puncture site and makes ambulatory procedures more feasible.

Microcatheters

Small flexible catheters, which can be passed through the lumen of a standard 5F catheter, have gained wide acceptance as a means of performing catheterization of small, more distal vessels (Fig. 1). Thus, chemoembolization of tumors in the liver or remote sites is now routine. These microcatheters can be used to deliver chemotherapeutic agents and can also deliver particles and coils to bleeding sites (8). Since these catheters are in the 2–3F range, they often have a gold or platinum bead on the catheter tip or on their guidewires to facilitate fluoroscopic observation.

Guidewires

Guidewires come in a variety of lengths, diameters, stiffnesses, and coatings. Most standard guidewires have a Teflon coating. It is important to remember that the distal tip of a wire may be straight or have a variety of distal J-like curves. Some wires have a shapeable distal tip. The other variable is the amount and length of softness ("floppiness") of the distal portion of a guidewire.

The standard diameters of guidewires are 0.035 and 0.038 inches. Microcatheters use

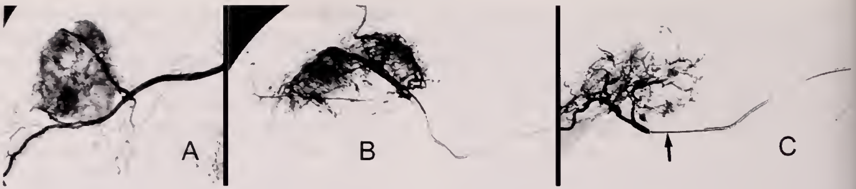

Fig. 1. Renal cell carcinoma metastatic to the humerus. Use of microcathether for preoperative embolization. **A.** Subclavian artery injection via 5F H1H catheter inserted via the right common femoral artery. The tumor is hypervascular. **B.** Large feeding branch entered with 5F catheter. Vessel was embolized with 350 micron polyvinyl foam particles. **C.** Small, more distal branch entered with microcatheter (arrow) placed through the 5F guiding catheter.

wires in the 0.010–0.018 inch range, depending on the choice of microcatheter. One of the major advances in angiography and guidewire design is the hydrophilic-coated guidewire. The best example of this is the Glidewire® (Terumo, Tokyo, Japan), which is available in a variety of lengths, diameters, and degrees of stiffness. This wire, which may have a straight or angled tip, has greatly increased our ability to traverse stenoses and manipulate through tortuous vessels, bile ducts and obstructed kidneys (9–11).

Sheaths and Guidecatheters

A majority of vascular procedures are performed through vascular access sheaths. The standard is 10 cm long, with a sidearm which allows continuous flush of saline to prevent clot formation between the sheath and the catheter. The catheters and guidewires are advanced through the sheath via a hemostatic valve. A major advantage of a vascular sheath is that repeated trauma to the puncture site is eliminated, because all necessary exchanges of catheters and wires can be made via the sheath.

Sheaths are now available in a variety of lengths, diameters, and shapes. They are constructed in such a way as to avoid kinking, even when passing through tortuous vessels. Some sheaths can be shaped before inserting them into vessels (Fig. 2).

Guidecatheters are preshaped catheters designed to be placed through standard vascular sheaths, so that they can provide access to target vessels for interventions. They tend to be cumbersome and require upsizing of the initial entry sheath. They have been progressively replaced by the previously described shaped vascular sheaths

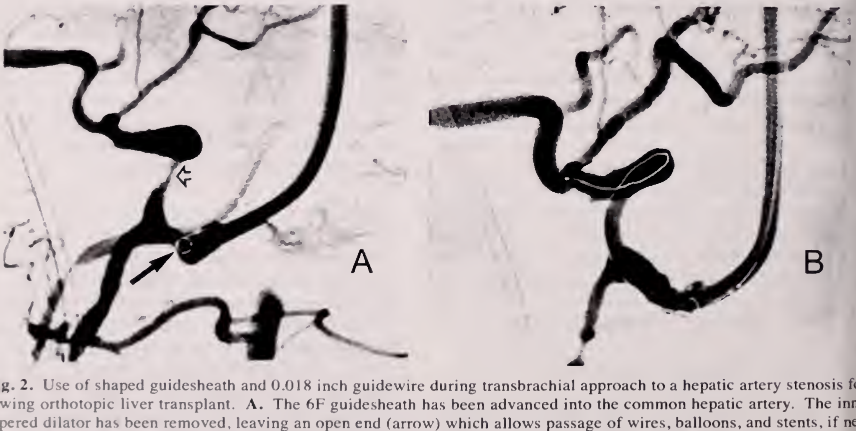

Fig. 2. Use of shaped guidesheath and 0.018 inch guidewire during transbrachial approach to a hepatic artery stenosis fo lowing orthotopic liver transplant. **A.** The 6F guidesheath has been advanced into the common hepatic artery. The inn tapered dilator has been removed, leaving an open end (arrow) which allows passage of wires, balloons, and stents, if ne essary. Note the stenosis (open arrow). **B.** An 0.018 inch wire is seen across the stenotic area, which has been balloon d lated. The vessels distal to the angioplasty site have dilated in response to the increased blood flow.

Conclusion

The diverse technology available for vascular and nonvascular interventions requires that the interventional radiologist, endovascular surgeon, neurointerventionalist, and interventional cardiologist be knowledgeable about products which change or are improved on a regular basis.

References

1. Tobis J, Johnston WD, Montelli S, et al. Digital coronary roadmapping as an aid for performing coronary angioplasty. Am J Cardiol 1985; 56(4):237–241.
2. Boland GW, Murphy B, Arellano R, et al. Dose reduction in gastrointestinal and genitourinary fluoroscopy: use of grid-controlled pulsed fluoroscopy. AJR Am J Roentgenol 2000; 175(5):1453–1457.
3. Waugh R, McCallum HM, McCarty M, et al. Pediatric pelvic imaging: optimization of dose and technique using digital grid-controlled pulsed fluoroscopy. Pediatr Radiol 2001; 31(5):368–373.
4. Fletcher DW, Miller DL, Balter S, Taylor MA. Comparison of four techniques to estimate radiation dose to skin during angiographic and interventional radiology procedures. J Vasc Interv Radiol 2002; 13:391–397.
5. Koenig TR, Mettler FA, Wagner LK. Skin injuries from fluoroscopically guided procedures: part 2, review of 73 cases and recommendations for minimizing dose delivered to patient. AJR Am J Roentgenol 2001; 177(1):13–20.
6. Andrews RT, Brown PH. Uterine arterial embolization: factors influencing patient radiation exposure. Radiology 2000; 21(3):713–722.
7. Lookstein RA. Impact of CT angiography on endovascular therapy. Mt Sinai J Med 2003; 70:367–374.
8. Doerfler A, Goericke S, Wanke I, et al. Flow-directed microcatheters for cerebral embolizations using Ethibloc — an in vitro study. Neuroradiology 2001; 43(12):1112–1117.
9. McFarlane JP, Cowan C, Holt SJ, Cowan MJ. Outpatient ureteric procedures: a new method for retrograde ureteropyelography and ureteric stent placement. BJU Int 2001; 87(3):172–176.
10. Park HS, Choo IW, Do YS, Choo SW. Migrated Hickman catheters: a simple repositioning method using a stiff hydrophilic guidewire. Cardiovasc Intervent Radiol 2000; 23(1):70–72.
11. Koizumi J, Mouri M, Watanabe M, Hiramatsu K. Transbrachial selective pulmonary angiography using a new 4 Fr curved pigtail catheter and hydrophilic-coated guidewire. Cardiovasc Intervent Radiol 1998; 21(4):347–349.

Duplex Ultrasonography and Its Impact on Providing Endograft Surveillance

VICTORIA J. TEODORESCU, M.D.[1], NICHOLAS J. MORRISSEY, M.D.[1], AND JEFFREY W. OLIN, D.O.[2]

Abstract

Increasingly, aortic aneurysms are being repaired using endoluminal grafting techniques. Complications of such surgery include persistent endoleaks, continued growth of the aneurysm and migration or thrombosis of the device. Consequently, patients undergoing endovascular repair must be under rigorous surveillance postoperatively. Spiral computed tomography scanning is the test of choice to assess the integrity of the repair, but frequent scanning subjects the patient to repeated doses of radiation and nephrotoxic contrast agents. Duplex ultrasound has long been used to diagnose the presence of aortic aneurysm and may be an appropriate tool for monitoring endovascular grafts. However, the wide variability in sensitivity, specificity, positive and negative predictive values, and accuracy rates described in the literature reflect the fact that many problems still exist with this technique. Until these difficulties can be resolved, duplex ultrasonography is best used in conjunction with spiral computed tomography.

Key Words: Duplex ultrasonography, aortic aneurysm, endograft repair.

SINCE ITS INTRODUCTION IN 1991 by Parodi et al. (1), endovascular repair of abdominal aortic aneurysms has been widely used. Yet collective experience has shown that although the procedure provides the benefits of less-invasive surgery and shorter length of stay, these advantages may be offset by late complications, such as persistent endoleak, continued growth of the aneurysm and even rupture (2, 3). Consequently, patients undergoing such treatment must remain under periodic surveillance to ensure continued integrity of repair. Spiral computed tomography (CT) is the test of choice, with scanning recommended in the early postoperative period, at 1 month and then at 6 month intervals, if no endoleaks are visualized (4). This rigorous testing schedule, however, subjects the patient to the risks of repeated doses of radiation and nephrotoxic contrast agents. Duplex ultrasonography (DU) is less expensive, easily obtainable and devoid of risks due to radiation or iodinated contrast agents. In addition, it is widely used as a tool to diagnose and follow abdominal aortic aneurysms. Thus, it may be an appropriate device for endograft surveillance.

Ten studies have been identified comparing CT and DU for postoperative evaluation of endovascular abdominal aortic aneurysm repair (5 – 14). The total number of patients studied was 804. In seven of these studies, the CT scan and DU were obtained within 7 days of each other. In two others, the time interval between the tests was not stated. The study reported by McLafferty et al. (13) is flawed because the CT scan and DU were not performed during the same time interval. Two hundred one endoleaks were identified in the 804 patients (25%). These reports indicate that DU accurately identifies the presence of endoleaks following endovascular repair of aneurysms, with an overall sensitivity of 93% (range 77 – 100%), specificity of 94% (range 74 – 100%), positive predictive value of 78% (range 66 – 100%), negative predictive value of 98% (range 90 – 100%), and accuracy of 93% (range 82 – 100%).

Theoretically, DU may be accurate in

---

[1] Assistant Professor, Division of Vascular Surgery, Department of Surgery, and [2] Director, Vascular Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Victoria J. Teodorescu, M.D., Department of Surgery, Box 1259, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Theoretically, DU may be accurate in identifying not only the presence of an endoleak, but its source as well. D'Audiffret was able to localize a potential source of filling by either the inferior mesenteric artery or a lumbar branch in all of the type 2 endoleaks identified (11). Such accuracy requires thorough examination by an experienced technician. Studies should be performed on a high-resolution duplex ultrasound machine. Examination of retroperitoneal structures requires the use of low-frequency curved array, phased array or mechanical sector, and pulsed Doppler scan transducers. Patients, who must have been fasting for a period of eight hours, are studied in the supine position. The entire aortic sac is examined, including the graft and its proximal and distal attachment sites, using the B-mode. Maximum diameter of the sac is obtained. Following this, color Doppler scan is obtained in both the transverse and longitudinal axes, avoiding both excessive overgain and undergain. Pulsatile color scan flow seen within the aortic sac but outside the graft may be indicative of endoleak. If an endoleak is suspected, attention should then be paid to the proximal and distal attachment sites, the inferior mesenteric artery, and the lumbar arteries. Spectral Doppler waveform analysis will help differentiate true endoleak from artifact and determine the direction of flow (Figs. 1–4).

There are limitations in the use of DU to evaluate endovascular grafts postoperatively. For example, integrity of the stent itself cannot be assessed by DU. Plain abdominal X-rays remain the test of choice to diagnose stent fracture. And, as with any other abdominal or retroperitoneal examination, excessive bowel gas will interfere with the ability to obtain a high-quality ultrasound.

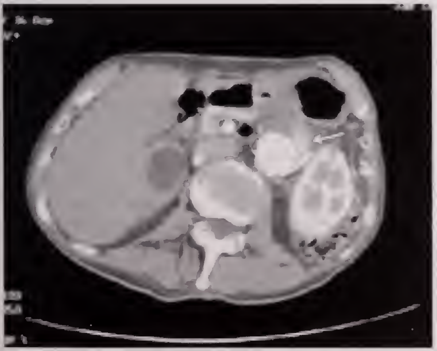

Fig. 1. Spiral computed tomography demonstrating an endoleak (arrow).

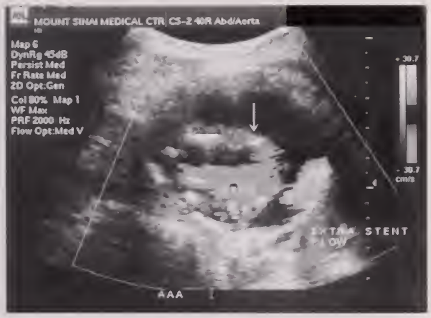
MOUNT SINAI MEDICAL CTR C5-2 40R Abd/Aorta
Map 6
DynRg 45dB
Persist Med
Fr Rate Med
2D Opt:Gen
Col 80% Map 1
WF Max
PRF 2000 Hz
Flow Opt:Med V
+ 30.7
- 30.7
cm/s
EXTRA STENT
FLOW
AAA

Fig. 2. Duplex ultrasonography of the same patient demonstrating the endoleak, labeled as "extra stent flow" on this image. A transverse image of the aneurysm has been obtained, similar to what is seen on computed tomography. The stent is visualized largely surrounded by thrombus (arrow). However, flow is seen outside the stent, indicating the presence of an endoleak.

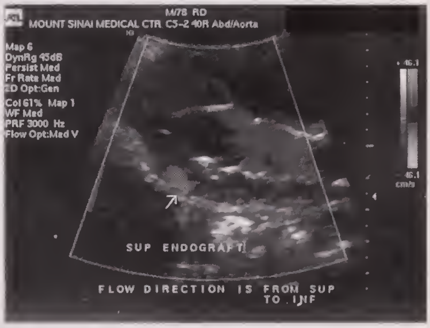
M/78 RD
MOUNT SINAI MEDICAL CTR C5-2 40R Abd/Aorta
Map 6
DynRg 45dB
Persist Med
Fr Rate Med
2D Opt:Gen
Col 61% Map 1
WF Med
PRF 3000 Hz
Flow Opt:Med V
+ 46.1
46.1
cm/s
SUP ENDOGRAFT
FLOW DIRECTION IS FROM SUP TO INF

Fig. 3. A longitudinal image of the aneurysm demonstrates leakage from the proximal attachment site of the graft. The direction of extra-stent flow (arrow) is from superior to inferior.

Summary

Spiral computed tomography is currently the best choice to evaluate the results of endovascular repair of abdominal aortic aneurysm. However, the necessary rigorous postoperative surveillance subjects the patient to repeated doses of radiation and nephrotoxic con-

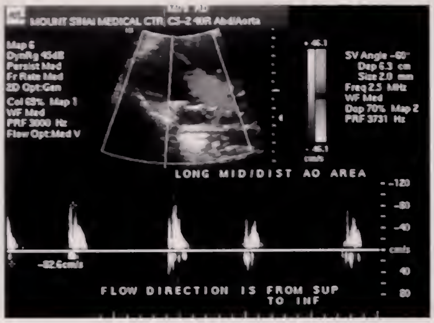

Fig. 4. Spectral Doppler waveform analysis confirms the presence of the endoleak. In addition, flow direction is determined by the deflection of the waveform above baseline.

trast agents. Duplex ultrasonography, a less expensive tool with no risk of nephrotoxicity or exposure to radiation, may yet prove to be a useful tool to follow patients assuming that the many problems can be resolved.

References

1. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991; 5(6):491–499.
2. Schurink GWH, Aarts NJM, van Bockel JH. Endoleak after stent-graft treatment of abdominal aortic aneurysm: a meta-analysis of clinical studies. Br J Surg 1999; 86(5):581–587.
3. Bernhard VM, Mitchell RS, Matumura JS, et al. Ruptured abdominal aortic aneurysm after endovascular repair. J Vasc Surg 2002; 35(6):1155–1162.
4. Karch LA, Henretta JP, Hodgson KJ, et al. Algorithm for the diagnosis and treatment of endoleaks. Am J Surg 1999; 178(3):225–231.
5. Heilberger P, Schunn C, Ritter W, et al. Postoperative color flow duplex scanning in aortic endografting. J Endovasc Surg 1997; 4(3):262–271.
6. Thompson MM, Boyle JR, Hartshorn T, et al. Comparison of computed tomography and duplex imaging in assessing aortic morphology following endovascular aneurysm repair. Br J Surg 1998; 85(3):346–350.
7. Kronzon I, Tunick PA, Rosen R, Riles T. Ultrasound evaluation of endovascular repair of abdominal aortic aneurysms. J Am Soc Echocardiogr 1998; 11(4):377–380.
8. Sato DT, Goff CD, Gregory RT, et al. Endoleak after aortic stent graft repair: diagnosis by color duplex ultrasound scan versus computed tomography scan. J Vasc Surg 1998; 28(4):657–663.
9. Fletcher J, Saker K, Baptiste P, Dyer S. Colour Doppler diagnosis of perigraft flow following endovascular repair of abdominal aortic aneurysm. Int Angiol 2000; 19(4):326–330.
10. Zannetti S, De Rango P, Parente B, et al. Role of duplex scan in endoleak detection after endoluminal abdominal aortic aneurysm repair. Eur J Vasc Endovasc 2000; 19(5):531–535.
11. D'Audiffret A, Desgranges P, Kobeiter H, Becquemin JP. Follow-up evaluation of endoluminally treated abdominal aortic aneurysms with duplex ultrasonography: validation with computed tomography. J Vasc Surg 2001; 33(1):42–50.
12. Wolf YG, Johnson BL, Hill BB, et al. Duplex ultrasound scanning versus computed tomographic angiography for postoperative evaluation of endovascular abdominal aortic aneurysm repair. J Vasc Surg 2000; 32(6):1142–1148.
13. McLafferty RB, McCrary BS, Mattos MA, et al. The use of color-flow duplex scan for the detection of endoleaks. J Vasc Surg 2002; 36(1):100–104.
14. Golzarian J, Murgo S, Dussaussois L, et al. Evaluation of abdominal aortic aneurysm after endoluminal treatment: comparison of color Doppler sonography with biphasic helical CT. Am J Roentgenol 2002; 178(3):623–628.

Impact of CT Angiography on Endovascular Therapy

Robert A. Lookstein, M.D.

Abstract

In the last ten years, computed tomography (CT) angiography has evolved from an experimental diagnostic tool to the preferred imaging study for a variety of disease processes. At the same time, endovascular surgery has become the first-line therapy for several types of peripheral vascular disease. With the recent introduction of multidetector computed tomography, CT angiography of the entire peripheral vascular system is possible in mere seconds. This imaging modality has become critical for the pre-procedure planning and post-procedure follow-up of several endovascular procedures, including endovascular aneurysm repair, lower extremity revascularization, and renal artery revascularization. A thorough knowledge of the current applications of CT angiography with respect to the peripheral vasculature is essential for the endovascular specialist.

Key Words: CT angiography, angiography, vascular imaging, endovascular therapy, minimally invasive.

Introduction

Computed tomography (CT) angiography has become the preferred screening tool for vascular disease since it was first described in 1992 (1). This study tool is faster and more minimally invasive than previous tools, making it the imaging modality of choice when planning endovascular procedures as well as when performing routine follow-ups of these patients. The recent technologic advancements with regard to multidetector CT (MDCT) have allowed this powerful imaging tool to perform more rapid imaging while at the same time permitting more coverage of the patient, with higher spatial resolution (Fig. 1). This article reviews the technical factors that must be taken into consideration in planning and interpreting CT angiograms (CTA), as well as the applications that are most relevant to the endovascular specialist.

Imaging Techniques

The most important step in CT angiography is determining the area of the patient to be imaged. With current commercially available systems, a reasonable area to be covered is the chest and abdomen down to the patient's knees, or the abdomen and pelvis down to the patients' feet. It is important to realize that most endovascular procedures are performed from the common femoral artery approach. As a result, routine imaging of this anatomic region is mandatory.

To guarantee that all relevant anatomy will be included, a noncontrast scout view may be obtained and reviewed in order to visualize certain landmarks to be imaged prior to angiography. Following this, an intravenous non-ionic bolus of contrast media, usually about 15 mL, is injected to time the delay between the injection and image acquisition. After the extent of the delay is determined, the angiogram can be performed. Typically, 80 – 100 mL of intravenous non-ionic contrast agent is administered at an injection rate of 4 – 5 mL/sec.

Clinical Applications

Aortic Aneurysm

Conventional angiography has long been the preferred technique for evaluating aortic aneurysms. While it is invasive, it is rarely associated with complications such as puncture site hematomas and arterial dissection. How-

---

Address all correspondence to Robert A. Lookstein, M.D., Assistant Professor of Radiology, Box 1234, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; Robert.Lookstein@mssm.edu

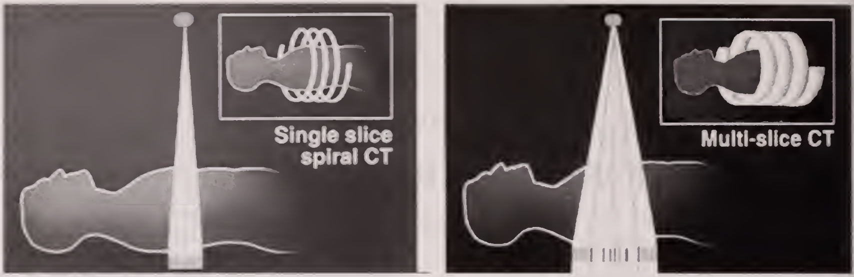

Fig 1. Diagrammatic representation of multidetector CT. Four channels are shown revolving around the patient as compared to one channel for single-detector helical CT. Multidetector CT allows more volume of the patient to be scanned in a shorter period of time. Diagram courtesy of Siemens Medical Systems.

ever, it is only able to indirectly detect mural thrombi within an aneurysm.

On the other hand, CT angiography is less invasive and more accurate in determining the true size of the aneurysm sac. It is also far superior in its ability to detect mural thrombus. CTA can directly visualize the wall of the aorta and the surrounding structures. This is of great importance when characterizing inflammatory aneurysms as well as aneurysm rupture. Moreover, CTA has been shown to accurately characterize juxtarenal or suprarenal extension of an abdominal aneurysm and to be highly accurate in the evaluation of branch vessel stenosis (2, 3) (Fig. 2).

Aortic Stent-Grafts

Until recently, open surgical repair was the only treatment option available for patients with abdominal aortic aneurysms. But, with the introduction and now widespread use of endovascular stent-grafts, patients once consid-

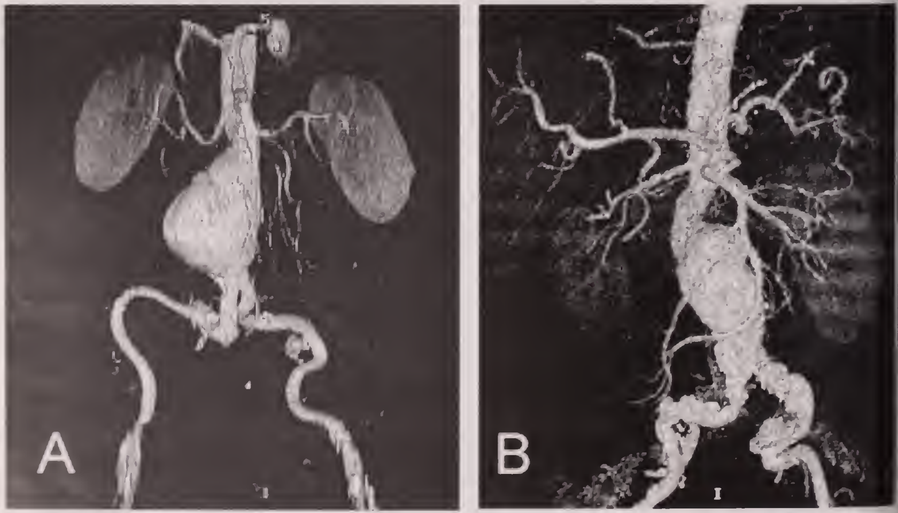

Fig. 2. (A) 3D reconstruction of a preoperative CTA of a patient being evaluated for endovascular repair. Note the poor spatial resolution of the branch vessels as well as the motion artifact at the bottom of the study. **(B)** 3D representation of a preoperative CTA on an 8-row multidetector CT. This study is able to characterize the vessels branching from the aorta and gives an accurate representation of the extent of the aneurysm.

ered poor surgical candidates are undergoing successful endovascular repair. The key to a successful outcome when using endovascular techniques is the ability to measure the maximum aneurysm diameter, the length of the abdominal aorta, and the degree of tortuosity of the aorta. These factors must be taken into consideration in the planning of these stent-graft procedures, since each stent-graft must conform to the patient's anatomy if complications are to be avoided. Routinely, a 15 mm proximal neck is required for adequate sealing of the vessel to the stent-graft. The endograft diameter is usually 2–3 mm larger than the vessel lumen. If the endograft diameter is too small or if the length of the proximal neck is too short, there may be an inadequate seal, which can lead to perigraft flow or endoleak. Too large a diameter may lead to folding of the endograft and an endoleak. Endografts that are too long or too short can lead to seal problems and ultimately to endoleaks, limb kinking or limb occlusion.

Transverse CT aortic measurements have been previously used to measure the diameter of the aorta. These measurements can greatly overestimate the true diameter because of obliquity. Similarly, craniocaudal measurements can substantially underestimate the true aortic length by not accounting for tortuosity.

One method of obtaining an accurate cross-sectional measurement is the creation of oblique multiplanar reformats perpendicular to the longitudinal axis of the aorta. This mean centerline can accurately determine the length of the aortic lumen that the endovascular device must cover, which is typically from the lowest renal artery to the origin of the internal iliac arteries bilaterally. A recent article examined this technique with respect to its accuracy in determining the length of the endovascular device (4). The article also described an algorithm used to determine the shortest path within the aortic lumen for the device to follow and demonstrated that the shortest path is the most accurate in predicting the true *in vivo* length of the device. Expanded use of this measurement may allow for more accurate preoperative measurements that can reduce the number of device-related complications. The median centerline can also give accurate luminal diameter measurements at any location along the aorta. Aortic length measurements of importance in the planning of these devices are the length from the lowest renal artery to the origin of the aneurysm, the length of the aneurysm itself, and the length from the aortic bifurcation to the origin of the internal iliac artery. Diameters of critical importance are those at the proximal attachment site at the lowest renal artery, the maximal diameter of the aorta, the diameter at the aortic bifurcation, and the diameter of the iliac arteries at the origin of the hypogastric artery.

Another parameter that can be determined using MDCT is the degree of tortuosity of the aneurysm. This variable can be critical in predicting the complexity of the procedure preoperatively and in choosing the site of primary access of the device. Wolf et al. reported that the degree of tortuosity correlated with increased complexity of the endovascular repair and with immediate device failure or endoleak (5).

Aneurysm volume has recently attracted a great deal of interest. This measurement has been theorized to be a more accurate method of detecting subtle postoperative changes in the aneurysm. A recent report demonstrated this measurement to be very powerful in its ability to predict endoleak (6). Volume changes can be detected earlier than diameter changes and can therefore be used to predict patients who are likely to have device failures (Fig. 3).

Postoperative Surveillance

CTA is very useful in the post-procedure monitoring of patients who have undergone endovascular repair of abdominal aortic aneurysm. The success of the treatment is dependant on continued exclusion of blood flow into the aneurysm sac. Persistent flow into the sac (or endoleak) is a sign of treatment failure. Because CTA relies on general arterial opacification, it is quite sensitive in detecting perigraft flow.

In 2000, Armerding et al. (7) studied the ability of helical CT to detect the presence of endoleak, as compared to conventional angiography. Forty patients underwent both helical CT and conventional angiography after stent-graft placement for abdominal aortic aneurysm. Twenty perigraft leaks were detected in the results of 46 examinations. CT was found to be more sensitive and specific than angiography.

When a CTA scan is performed postoperatively, it is imperative that prior administration of contrast be withheld in order to differentiate the presence of calcium within the sac thrombus from any true perigraft enhancement. Immediately following this examination, the scan can be repeated with contrast. This technique has been shown to increase the sensitivity of the study in detecting endoleaks (Fig. 4).

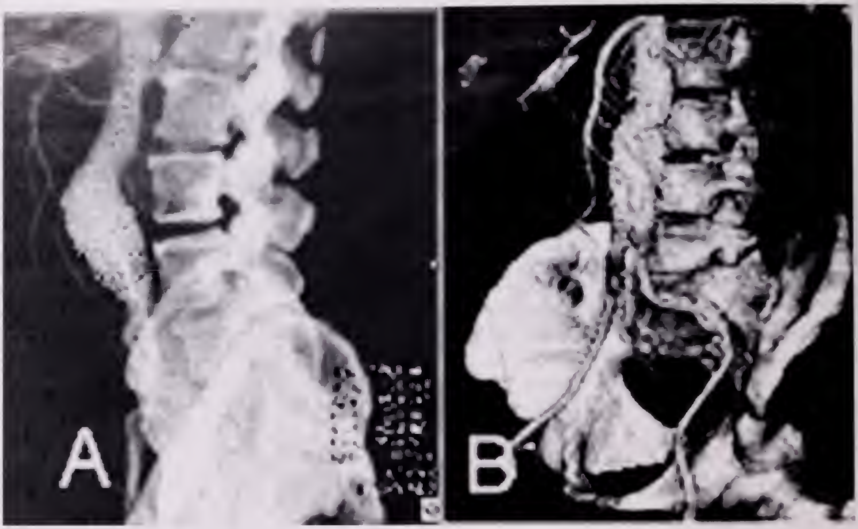

Fig. 3. (A) Median Center Line program determines length of the endovascular device from the renal artery to the internal iliac artery origin, as well as maximum and minimal luminal diameter. **(B)** A 3D data set of an infrarenal aneurysm in which the surface area (112 cm^2) and volume (81 mL) of the aneurysm have been calculated. This information can be used to compare with postoperative studies to monitor the success of the endovascular repair.

The current classification used by the American Association of Vascular Surgeons (AAVS) to describe endoleaks is:

- Type 1 endoleak is caused by an incomplete seal at the proximal or distal attachment site or at the site of an iliac occluder device. It is relatively uncommon.

- Type 2 endoleak results from retrograde filling of the aneurysm sac from a patent branch vessel. It is the most common type of endoleak. The most frequent sources of type 2 endoleaks are via the inferior mesenteric artery and/or the iliolumbar artery to a lumbar artery arising off the sac.

- Type 3 endoleak is due to a tear in the fabric of the device from shear stress or from a fracture of one of the metallic struts of the framework. It is rare.

- Type 4 endoleak occurs when there is flow through the fabric of the graft due to increased porosity. It is very rare but is seen with Dacron grafts. It is usually a transient phenomenon occurring immediately after implantation of the graft, and resolves after a few days (8).

3D reconstruction of MDCT data sets is extremely helpful for the postoperative evaluation of these patients. The 3D image processing allows excellent visualization of aneurysm and endograft deformation. Endograft deformation leading to type 1 and 3 endoleaks may result in catastrophic consequences, including aneurysm rupture. 3D reconstruction can also aid in the characterization of endoleak by delineating the inflow or outflow sources (Fig. 5).

As mentioned above, measuring the volume of the aneurysm can be an effective method of following up with these patients. A recent article (9) reported that successful treatment correlates with deceasing volume of the aneurysm, and that patients whose aneurysms do not decrease in volume may be at risk for endoleak formation.

A typical recommended schedule of follow-up studies includes 1 month after the procedure, 6 months after the procedure, 1 year after the

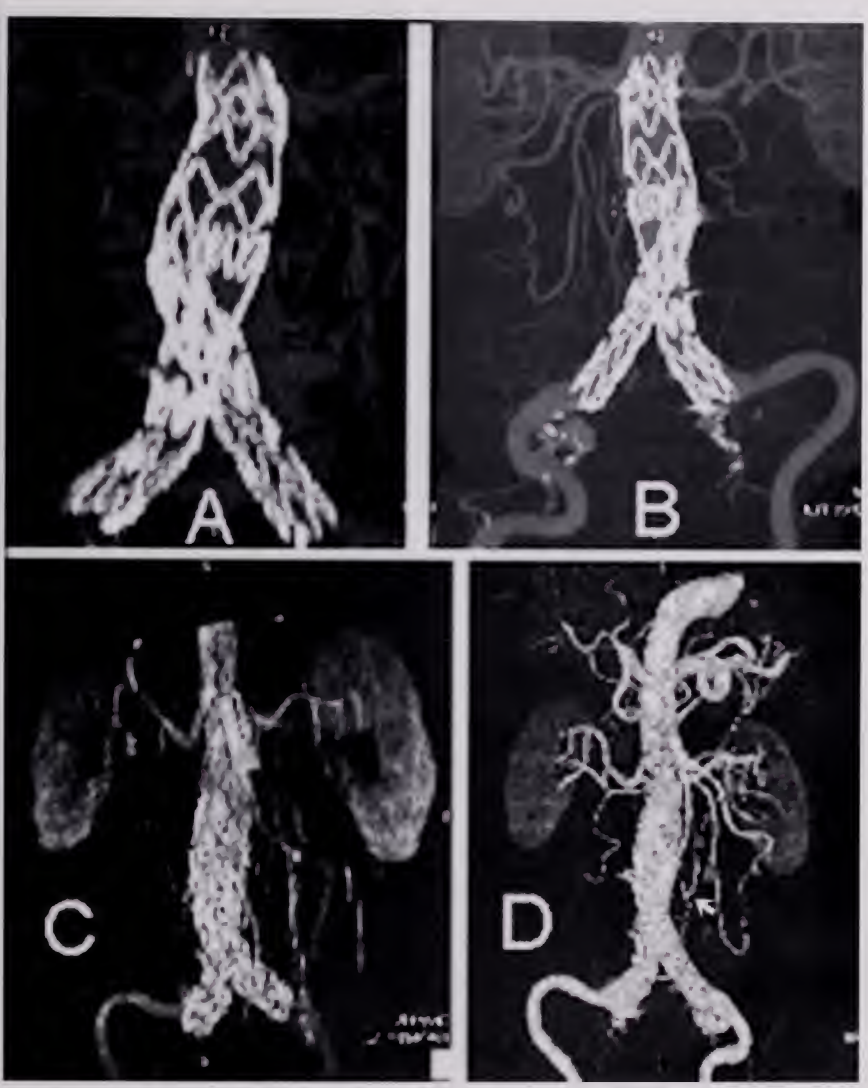

Fig. 4. (A) 3D reconstruction with single-row helical CT. The image is windowed to allow visualization of the metallic stent framework of the aortic endoprosthesis. **(B)** 3D reconstruction with 8-row multidetector CT (MDCT) of same patient. Notice excellent visualization of the stent framework, as compared to previous study. **(C)** Postoperative study of the same patient with a single-detector helical CT. **(D)** Postoperative CTA of same patient with 8-row MDCT. Notice exquisite resolution of the aortic vasculature. There is excellent detail of all aortic branches and the endovascular device. There is a suggestion (arrow) of perigraft flow or endoleak anterior to the device.

procedure, and then yearly. For patients in whom an endoleak is identified, the interval decreases to 3 months in order to monitor the stability of the leak and possibly plan future intervention.

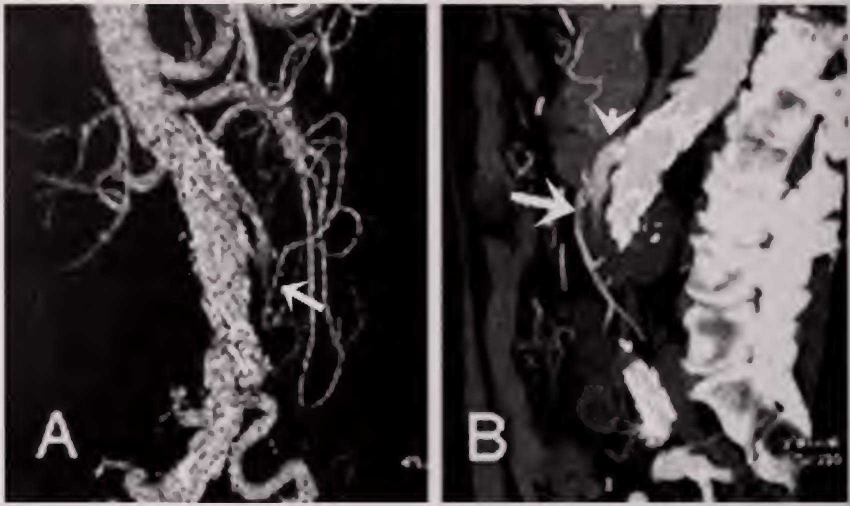

Fig. 5. (A) Right anterior oblique projection of same data set from Fig. 4 demonstrates perigraft flow in communication with the inferior mesenteric artery probably representing a Type 2 endoleak (arrow). **(B)** Curved multiplanar reformat of a maximum intensity projection shows the endoleak (arrowhead) to directly communicate with the inferior mesenteric artery (arrow).

Lower Extremity Occlusive Disease

A great deal of interest has arisen over a noninvasive method of screening for lower extremity vascular disease. While duplex sonography and plethysmography are quite reliable in identifying and localizing the general anatomic region involved, these tests cannot be used alone in planning endovascular procedures for the lower extremities. The specificities of these examinations are diminished in the presence of multilevel disease.

CTA has recently emerged as an attractive alternative for the screening of patients with presumed lower extremity occlusive disease as well as for those planning possible endovascular treatment. It is important to realize that the region of interest in these studies must be more than one meter in length, so as to include images depicting both inflow and runoff.

Single-detector spiral CT cannot provide imaging of the entire lower extremity. In 1995, Lawrence et al. reported imaging a portion of the lower extremity from the groin to the proximal calf in six patients with single-detector spiral CT angiography. The patients were studied with 5 mm slices. The studies were performed over an area of interest of 60 cm and took more than two minutes to acquire (10). A later study performed by Beregi et al. imaged the popliteal arteries in patients suspected of having popliteal artery disease. This study demonstrated increased sensitivity and specificity in the detection of patients with popliteal artery aneurysms, as well as improved characterization of arterial compression by adventitial cysts and entrapment syndromes (11).

MDCT has three primary advantages over single-row detector CT: shorter scanning durations, thinner sections of entire anatomic territories, and greater longitudinal coverage.

A recent study by Rubin et al. used MDCT angiography on 24 patients with symptomatic lower extremity occlusive disease. The study used 2.5 mm slices to acquire images extending from the abdominal aorta to the feet. The average study time was a little over one minute and covered 1.2 meters. This study demonstrated a 100% concordance between CT and conventional angiography at direct comparison (12).

Our current protocol includes 2 mm slices from the diaphragm to the feet with a 16 row MDCT. Our studies take less than 30 seconds to acquire (Fig. 6).

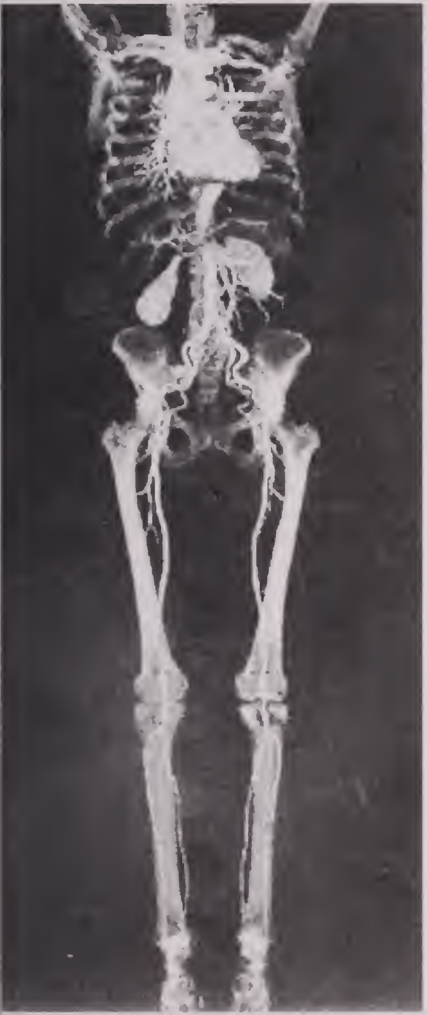

Fig. 6. Whole body CT angiogram performed on a 16-row multidetector scanner. This study was performed from the carotid arteries down to the feet in less than one minute.

Renal Arteries

Renovascular hypertension and ischemic nephropathy have become topics of interest to all endovascular specialists, with the increasing use of endovascular stent technology to treat these conditions. One limitation of CT angiography is the fact that the renal arteries typically course in the plane of the axial sections in which the data is collected.

A study designed to visualize the renal arteries should include not only the abdominal aorta but also the iliac and femoral arteries bilaterally, since these are the approaches used in the treatment of this disease entity.

Many studies have been performed to analyze the utility of CT angiography in the diagnosis of renal artery stenosis. In 1994, Galanski et al. reported a comparison of single-detector helical CTA with conventional angiography and found that the former technique provided the correct identification of renal artery stenosis in 22 of 54 renal arteries examined. Demonstration of the degree of stenosis was found to be comparable to that with conventional angiography in all but four patients (13). When compared to conventional angiography, the sensitivity and specificity of CTA was 92% and 95% respectively.

In 1997, Kaatee reported an important study which showed that false positive diagnoses of renal artery stenosis were in fact false negative studies during conventional angiography performed in suboptimal projections (14) Specifically, the techniques for conventional angiography did not optimally visualize the renal arteries and missed several stenoses. Other studies have shown that ancillary findings that may aid in the diagnosis of renal artery stenosis include post-stenotic dilatation and asymmetric renal parenchymal enhancement. The presence of renal artery calcification has not been shown to correlate strongly with renal artery stenosis.

A recent study by Behar et al. compared CTA and conventional angiography for the follow-up of patients who had undergone renal artery stent placement. In a total of 15 patients, all 17 stent lumina were well visualized. The CT angiograms appeared to underestimate the lumen of the vessel slightly as compared to conventional angiograms. The cause for this was unknown (15) (Fig. 7).

Summary

The imaging requirements for endovascular procedures are much more complex than those previously required for open vascular procedures. Many details must be evaluated before the physicians can select those procedure(s) and devices that will optimize the outcome. Poor planning usually results in a technical failure, with the need for repeat procedures or (ulti-

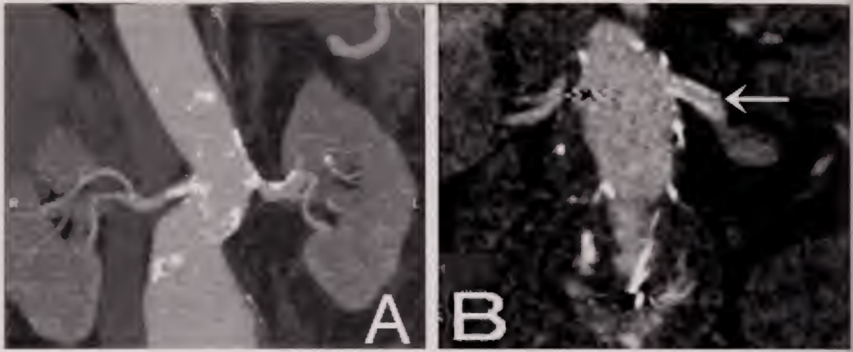

Fig. 7. (A) 3D reconstruction of a CTA of the abdomen. The patient is noted to have a left renal artery stenosis. **(B)** Coronal section of a Maximum Intensity Projection MultiDetector CTA data set in a different patient who had undergone left renal artery stenting. The lumen of the left renal artery can be visualized on this study and is noted to be patent (arrow).

mately) conversion to an open surgery. As a result, post-procedure imaging is essential for monitoring the success of the procedure and planning any further interventions. The endovascular specialist must be well versed in the latest imaging technology, in order to achieve technical success and adequately follow up patients who have undergone these minimally invasive procedures.

References

1. Napel S, Marks MP, Rubin GD, et al. CT angiography with spiral CT and maximum intensity projection. Radiology 1992; 185(2):607–610.
2. Van Hoe L, Baert AL, Gryspeerdt S, et al. Supra- and juxtarenal aneurysms of the abdominal aorta: preoperative assessment with thin-section spiral CT. Radiology 1996; 198(2):443–448.
3. Rubin GD, Walker PJ, Dake MD, et al. Three-dimensional spiral computed tomographic angiography: an alternative imaging modality for the abdominal aorta and its branches. J Vasc Surg 1993; 18(4):656–664.
4. Tillich M, Hill BB, Paik DS, et al. Prediction of aortoiliac stent-graft length: comparison of measurement methods. Radiology 2001; 220(2):475–483.
5. Wolf YG, Tillich M, Lee WA, et al. Impact of aortoiliac tortuosity on endovascular repair of abdominal aortic aneurysms: evaluation of 3D computer-based assessment. J Vasc Surg 2001; 34(4):594–599.
6. Lee JT, Lee J, Aziz IN, et al. Volume regression of abdominal aortic aneurysm and its relation to successful endoluminal exclusion (Abstract). Presented at the 56th Annual Scientific Meeting of the Society of Vascular Surgery. Boston (MA). June 2002.
7. Armerding MD, Rubin GD, Beaulieu CF, et al. Aortic aneurysmal disease: assessment of stent-graft treatment-CT versus conventional angiography. Radiology 2000; 215(1):138–146.
8. Chaikof EL, Blankensteijn JD, Harris PL, et al. Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery of The Society for Vascular Surgery / American Association for Vascular Surgery. Revised reporting standards for endovascular aortic aneurysm repair. J Vasc Surg 2002; 35(5):1048–1060.
9. Pollock JG, Travis SJ, Whitaker SC, et al. Endovascular AAA repair: classification of aneurysm sac volumetric change using spiral computed tomographic angiography. J Endovasc Ther 2002; 9(2):185–193.
10. Lawrence JA, Kim D, Kent KC, et al. Lower extremity spiral CT angiography versus catheter angiography. Radiology 1995; 194:903–908.
11. Beregi JP, Djabbari M, Desmoucelle F, et al. Popliteal vascular disease: evaluation with spiral CT angiography. Radiology 1997; 203:477–483.
12. Rubin GD, Schmidt AJ, Logan LJ, Sofilos MC. Multi-detector row CT angiography of lower extremity arterial inflow and runoff: initial experience. Radiology 2001; 221(1):146–158.
13. Galanski M, Prokop M, Chavan A, et al. [Accuracy of CT angiography in the diagnosis of renal artery stenosis] [German]. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1994; 161(6):519–525.
14. Kaatee R, Beek FJ, de Lange EE, et al. Renal artery stenosis: detection and quantification with spiral CT angiography versus optimized digital subtraction angiography. Radiology 1997; 205(1):121–127.
15. Behar JV, Nelson RC, Zidar JP, et al. Thin-section multidetector CT angiography of renal artery stents. AJR Am J Roentgenol 2002; 178(5):1155–1159.

New Techniques and Applications for Magnetic Resonance Angiography

JEFFREY P. GOLDMAN, M.D.

Abstract

Recent technological advances in magnetic resonance imaging have transformed the field of magnetic resonance angiography (MRA) from a research tool into an important clinical examination that is gaining acceptance as the screening modality of choice in evaluation of vascular disease. This article describes some of the new techniques and applications of MRA in clinical practice today.

Key Words: Magnetic resonance angiography.

Introduction

THE INTRODUCTION OF contrast-enhanced magnetic resonance angiography (CE-MRA) has catapulted tomographic magnetic resonance angiography (MRA) from an occasional adjunct examination into a robust tomographic imaging modality that plays an important role in the day-to-day evaluation of patients with vascular disease. CE-MRA follows the paradigm of X-ray angiography. Imaging is obtained after intravenous administration of a contrast agent as is done in X-ray angiography. The advantages of magnetic resonance angiography compared to X-ray angiography include:

- Noninvasiveness — instead of requiring intra-arterial injection of contrast (as in X-ray angiography), the agent is injected intravenously.
- Lack of ionizing radiation.
- Lack of a nephrotoxic contrast agent.

Noninvasive imaging, including MRA, is increasingly replacing diagnostic X-ray angiography in screening for vaso-occlusive disease. MRA is being used more widely in vascular imaging to provide a preoperative roadmap. In our institution, MRA is the sole preoperative modality used in imaging the arterial and venous vasculature for renal and liver transplant donors.

Contrast-Enhanced MRA — Imaging Technique

Contrast-Enhanced MRA versus Time-of-Flight MRA

Before the advent of CE-MRA, the major MRA technique was time-of-flight (TOF) imaging. CE-MRA overcomes many of the limitations and artifacts inherent in TOF-MRA. These include lack of artifacts due to cardiac pulsation, insensitivity to in-plane flow, and the lack of respiratory artifact since imaging is acquired within a breath-hold. If done correctly, contrast-enhanced CE-MRA is a much more robust technique than TOF-MRA. High-quality MRA images are obtained in more than 95% of examinations (1).

Contrast-Enhanced MRA versus Computed Tomography Angiography

Both contrast-enhanced computed tomography (CTA) and CE-MRA employ similar imaging paradigms, i.e., imaging the vessel lumen after the administration of an intravenous contrast agent. The advantages of MRA over CTA

Address all correspondence to Jeffrey P. Goldman, M.D., Clinical Director, Cardiovascular and Body MRI, Assistant Professor of Radiology, Department of Radiology, Box 1234, Mount Sinai School of Medicine, One East 100th Street, New York, NY, 10029.

is the lack of radiation, the use of an agent which is non-nephrotoxic, increased signal-to-noise ratio, and easier 3D postprocessing. Advantages of CTA over MRA include increased spatial resolution and easier image acquisition (CT is technically easier to perform than MR).

Imaging Pulse Sequence

Contrast-enhanced MRA is performed utilizing 3D spoiled gradient-echo imaging sequence. The advantage of this sequence is that it is a 3D sequence and reconstruction can be obtained in any plane. 3D as opposed to 2D gradient-echo images permits thinner, higher resolution images to be obtained within a breath-hold.

Contrast Agent

Gadolinium, one of the "rare earth" elements is a paramagnetic agent which increases the magnetic field adjacent to the gadolinium molecule. This shortens the T1 relaxation time of any substance in the region of the gadolinium molecule and enhances the MR signal intensity of blood on the T1-weighted postcontrast images. This contrast mechanism creates true anatomic images of vascular lumen, analogous to conventional angiography. There is no detectable toxicity to gadolinium and it can be used in patients with renal failure (2, 3). The dosage of gadolinium ranges from 0.1 – 0.3 mMol/kg IV (4). Gadolinium is excreted by the kidneys, and its half life is 1.5 hours.

Contrast Administration

Optimal contrast of arterial vasculature is produced by timing the acquisition of the MR images with the arrival of the contrast bolus in the arterial vasculature being imaged. A tight contrast bolus is improved by using a power injector (2 – 2.5 mL/sec).

Timing of Contrast Administration

The importance of accurately timing the delivery of the contrast bolus with image acquisition cannot be overemphasized. If imaging is begun too early, no contrast will be seen in the vessel. If imaging is begun too late, the contrast will already have washed out of the vessel being imaged and the venous system will be visualized. Multiple methods are available to optimize timing, and a considerable amount of research is being conducted to perfectly match the contrast bolus with data acquisition. Timing bolus techniques include:

- The "best guess" method — where an educated guess is made as to when contrast arrives in the vascular territory being imaged. The accuracy of this technique is on the order of 85%.
- Automated timing bolus — image acquisition begins when the contrast bolus is automatically detected in the vessel to be imaged. The success of this technique in our experience is about 85%.
- Timing bolus — 2 mL of gadolinium is injected at a prescribed injection rate using a power injector, followed by a 20 mL saline flush. Axial imaging is performed in the middle of the imaging volume using a fast gradient-echo sequence at an imaging rate of one frame per second. The time from the start of contrast injection to the peak arterial contrast is then calculated and used as the delay time for scanning to begin (5).

3D Reconstructions

One of the strengths of CE-MRA is acquired images are thin enough so that 3D reconstructions can be obtained. This allows rotation of the imaging volume in space. In order to rotate the volume without image distortion, images need to be acquired as an isometric imaging volume with resolution equal in all planes.

Optimization of 3D Gradient-Echo Imaging Parameters

The most common causes of a failed CE-MRA examination include:

- inability to maintain a breath-hold
- poor arterial phase timing, and
- inadequate coverage of the necessary imaging volume.

The ideal scan time of 15 – 20 sec allows most patients to maintain breath-hold. The following imaging parameters need to be optimized for each examination. Time to repetition and time to echo in spin (TR/TE) is minimized in order to maximize imaging speed. If one maintains a fixed scan time of less than 20 seconds while imaging a fixed volume one must compromise between higher image resolution and lower signal-to-noise ratio in adjusting the following parameters:

1. **Slice thickness** — thinner slices yield higher resolution but increase the number of

slices needed to cover the necessary volume, and decrease the signal-to-noise ratio per voxel. We try to maintain slice thickness of 3 mm or less.

2. **Matrix** — the higher the matrix, the higher the resolution, but the longer the scan time. We try to maintain matrices of 256 X 192 or 256 X 160.

3. **Bandwidth** — increasing bandwidth decreases scan time but also decreases signal-to-noise (S/N) ratio.

Advanced Concepts in CE-MRA

Understanding Basic K-Space

K-space is a very difficult concept for the non-physicist to understand. Simply, K-space is a spatial representation of the acquired MRI data. These MRI data can be acquired with different acquisition strategies which can and do affect the resultant image. After the MRI is performed, the K-space map is converted to an image by performing a mathematical process called a Fourier transformation which determines the spatial frequency features of the image. Each row of data in K-space represents an echo at a particular phase encoding step. The low-amplitude gradients, those with values near the center, provide the greatest contrast and signal.

Low spatial frequency information in the data within the center of K-space, determines image contrast. To have an arterial phase image in which arteries are bright and veins are dark, it is essential that the low spatial frequency data are acquired when a tight gadolinium bolus is present within the arteries being imaged and that the adjacent veins are dark.

High spatial frequency data at the periphery of K-space determines image detail. The presence of contrast is not as important for acquisition of peripheral K-space data, and this portion of K-space may be acquired before or after the contrast bolus is present within the arteries being imaged.

K-Space Artifacts

An important property of 3D gradient-echo imaging is its ability to alter the timing as to when the low-amplitude frequency data and the high-amplitude frequency data are being collected within the imaging sequence (6, 7).

1. **Early-timing artifact.** Hollow vessel or “ringing” artifact occurs when the low-frequency central portion of K-space is collected before the contrast bolus has reached its peak concentration and contrast concentration is still rapidly changing. The peripheral, high-frequency lines of K-space that determine the vessel edge, are less affected by the contrast bolus. The high-frequency data shows the vessel wall. The low-frequency contrast information shows a hollow vessel. This artifact is most common when using elliptical centric and centric ordering of K-space, since these acquisition strategies have a smaller window for acquiring the central low-frequency data of K-space. The tighter the contrast bolus (which occurs with faster injection of contrast and the shorter the imaging time), allows for a smaller the window for catching the contrast bolus at peak concentration. The hollow vessel artifact occurs when there is a mismatch in acquiring the central portion of K-space and the peak arterial contrast bolus of the vessel being imaged (3).

2. **Late-timing artifact.** If the central portion of K-space is imaged after the peak arterial phase has passed, venous contamination and lower signal to noise ratio will be seen in the image.

K-Space Acquisition Strategies

These techniques can be thought of as various strategies to adjust the “window” in time when the low-frequency data of K-space is collected. The scan delay must then be adjusted so that the tight contrast bolus is imaged at the precise time when the low- frequency data of K-space is collected.

1. **Sequential-phased-encoding ordering of K-space.** This is the traditional, most frequently used ordering of K-space acquisition. In this method lines of K-space are acquired sequentially. The central low-frequency data of K-space is acquired at the mid-portion of the image acquisition. The advantage of this method is that it is most forgiving and causes the least number of timing artifacts. When using sequential phased-encoded ordered K-space, the imaging delay can be calculated as follows (8):

Imaging delay = (contrast travel time) + $\frac{1}{2}$(injection time – imaging time)

2. **Centric-phased-encoding ordering of K-space.** In this strategy, the center low-frequency lines of K-space are acquired at the beginning of the scan. The advantage of this ordering of K-space is that if the patient breathes after 50% of the data has been collected, there will be less motion artifact. The arterial image should also have less venous contamination. When using centric-phased encoding ordering of K-space, the imaging delay is equal to the contrast travel time — the time from injection to when the contrast is first seen. This requires no additional calculation. The disadvantage of centric ordering of K-space is that it is more prone than sequential-phased-encoding ordering to mistiming artifacts (7).

3. **Elliptical-centric-phased-encoding ordering of K-space.** In this strategy, the center low-frequency lines of K-space are acquired at the beginning of the scan in an elliptical rather than linear manner. The advantage of this technique is that it covers the center of K-space very quickly with the least chance of venous contamination. For this reason, this technique is used in contrast-enhanced carotid MRA and moving-table-bolus chase peripheral MRA. When using elliptical-centric-phased-encoding ordering of K-space, the imaging delay is equal to the contrast travel time — the time from injection to when the contrast is first seen. The disadvantage of elliptical-centric-phased-encoding ordering of K-space, is that it is very sensitive to timing artifacts due to its very small temporal window during which K-space data are acquired. For this reason, we add one to two seconds to the contrast travel time (9).

4. **Reverse elliptical-phased-encoding ordering of K-space.** In this strategy, the low-frequency center lines of K-space are acquired at the end of the image acquisition.

5. **3D time-resolved imaging of contrast kinetics.** An increasing number of clever strategies are being developed to take advantage of the fact that it is not necessary to collect the entire portion of K-space in order to reconstruct an image. 3D time-resolved imaging of contrast kinetics (TRICKS) is a very clever technique which takes advantage of the fact that in a dynamic angiographic image the vessel edges or periphery of K-space do not change with time. What changes are the center low-frequency lines of K-space as the contrast bolus passes through the examined artery. In this technique the center portion of K-space is updated every 2–8 seconds, with the periphery of K-space being filled in at a later time. This has led to the term "time resolved" MRA. In this stratagem precise bolus timing is not necessary because the image is updated every 2–8 seconds. A "perfect" arterial phase should be present during at least one acquisition. The other advantage of this technique is that it begins to approach angiography in providing dynamic images in the flow of contrast (10).

Other Advanced MRA Techniques

1. **Time-resolved contrast-enhanced MRA.** New fast imaging techniques are available to increase the acquisition technique of a 3D MR angiogram to from 0.3 – 5 seconds. Though this technique is performed at lower spatial resolutions, the enhanced temporal resolution has advantages. At this temporal resolution, information regarding the temporal filling of vessels can be obtained. Initial studies have shown this technique is useful in evaluating patients with congenital heart disease, aortic stent-graft endoleaks, and peripheral vascular disease (2, 10).

2. **Moving-table-bolus chase MRA.** Moving-table-bolus chase MRA was introduced as a concept paralleling conventional angiography. In this technique, after acquiring a 3D CE-MRA of one vascular bed, the table is moved and imaging of a second vascular bed is performed while the contrast agent is still in the arterial bed. This strategy is routinely used in peripheral vascular MRA. We have also been using this technique in imaging of the entire aorta, to allow visualization down to the iliac vessels (11) (Fig. 1).

3. **Black blood imaging.** As opposed to CE-MRA, where flowing blood within a vessel is bright, in "black blood imaging" the signal intensity of flowing blood is suppressed, producing an image where the vessel lumen is black (12). Since the vessel lumen is black and the vessel wall is bright, black blood imaging allows for excellent imaging of the vessel wall. This is useful in evaluation of aortic dissection, intramural hematoma, penetrating ulcer, aortitis and

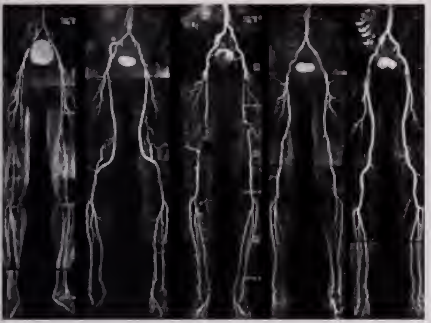

Fig. 1. Five examples of moving-table-bolus chase peripheral MRA. illustrate how a contrast bolus can be followed from the aortic bifurcation to the feet while minimizing venous contamination.

atherosclerotic plaque. The current limitation of black blood techniques is the increased duration of the examination. New sequences for multislice black blood imaging are being developed by different vendors.

4. **Bright blood imaging.** Bright blood image is especially useful for imaging of the vessel lumen (13). CE-MRA is a bright blood imaging technique. Steady-state free procession imaging (SSFP) is a new technique which produces high resolution bright blood imaging without administering intravenous contrast agent. This technique can be used to provide high temporal and spatial resolution images of a vessel or of the heart. These images can be viewed in a cine mode which allows for visualization of cardiac contraction. Bright blood SSFP also provides high resolution cine imaging of the vessel wall. These images are useful in evaluation of dissection and aortic aneurysms.

Applications of CE-MRA

Coronary artery disease and peripheral vascular disease are two major causes of morbidity, mortality and rising health costs in this country. Atherosclerosis appears to be the common link between these two disease processes. Remodeling of the vascular wall secondary to the atherosclerotic process results in the development of aneurysmal changes. Traditionally, surgery has been the treatment of choice for the correction of aneurysms of the aorta and peripheral arteries. Advances in minimally invasive and endovascular therapy have provided additional avenues of treatment and have potentially reduced morbidity, mortality, lengths of stay in the hospital, and costs to the already overburdened health care system. Due to the diffuse nature of the atherosclerosis process, many patients also have associated vascular complications such as diffuse atherosclerotic plaques and renal insufficiency. A noninvasive and nonnephrotoxic imaging technique for the pre- and post-interventional evaluation of the diseased vessels and the placement of the endovascular stent-grafts will greatly reduce the potential risks and dangers associated with conventional X-ray contrast angiography. Magnetic resonance imaging (MRI) has emerged as a highly attractive imaging modality for the routine follow-up evaluation of patients with peripheral vascular disease.

Clinical Indications for MRA

1. To screen for vaso-occlusive disease — carotid arteries, arch vessels, renal arteries, peripheral vessels.
2. To evaluate the anatomy of the aortic valve and origin of the coronary arteries.
3. Preoperative planning for repair of abdominal aortic aneurysms.
4. Postoperative follow-up of aortic aneurysm repair.
5. Preoperative planning to repair thoracic aortic aneurysms.
6. Postoperative follow-up of thoracic aortic aneurysm repair.
7. To image aortic dissection.
8. To image vasculitis.

Screening for Vaso-occlusive Disease

1. **Carotid artery stenosis.** Currently, digital subtraction angiography (DSA) is considered the best for detecting and grading carotid stenosis, but the associated risk of stroke is between 0.7 – 1.0% (14). For this reason, noninvasive imaging would be desirable. The sensitivity of MRA in detection of carotid artery stenosis ranges from 75 – 100%, while its specificity ranges from 59 – 99% (10, 15, 16). Recent studies have suggested that CE-MRA improves the sensitivity and specificity for detection of carotid artery stenosis over that of time-of-flight imaging. Cosottini et al. have shown that while CE-MRA still overestimates stenosis, the results indicated that it had limited value as a tool for preoperative evaluation of carotid artery stenosis (17).

2. **Arch vessels.** MRA and CTA are accepted screening modalities for the carotid arteries and arch vessels (18, 19) (Fig. 2).

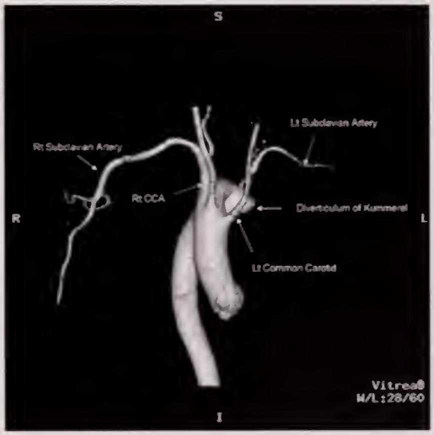

Fig. 2. Contrast-enhanced MRA of aberrant left subclavian artery with diverticulum of Kummerel.

3. **Renal arteries.** CE-MRA has special advantages over DSA or CE-CTA in evaluation of renal artery stenosis (RAS) in that the contrast agent is nonnephrotoxic and can be used to study patients with renal failure. Clinical indications for CE-MRA of the renal arteries are renal transplant donors, uncontrollable hypertension and ischemic renal nephropathy (Figs. 3 and 4). CE-MRA compares favorably to DSA in many studies showing a sensitivity of greater than 96% in most studies with specificity greater than 92% (20–23). In many centers, MRA is the screening modality of choice for suspected RAS.

4. **Peripheral vasculature.** Prevalence of peripheral vascular disease is about 7% for people older than 50. The most common symptoms of peripheral vascular occlusive disease are claudication (pain with exercise) or rest pain, depending on the distribution of the disease. Therapeutic interventions include angioplasty, stenting, surgical revascularization and bypass grafting. Flow-limited stenosis can occur anywhere between the aorta and foot. The goal of noninvasive imaging is to provide a "roadmap" for the vascular surgeon or interventional radiologist. The challenge of imaging the peripheral vasculature is the large territory that must be covered. Imaging from the aortic bifurcation to the trifurcation vessels can be obtained routinely. High resolution imaging of the feet without venous contamination using a single injection technique is more challenging.

Evaluation of the Aortic Valve and Origin of the Coronary Arteries

Breath-hold cine images may be obtained in two planes for evaluation of the aortic valve. We perform this routinely in the work-up of as-

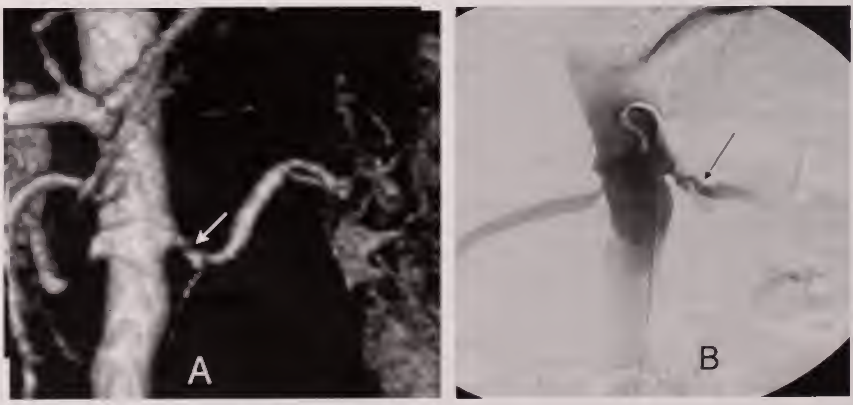

Fig. 3. (A) MRA left renal artery stenosis (arrow). (B) Corresponding X-ray angiogram shows left renal artery stenosis (RAS) (arrow).

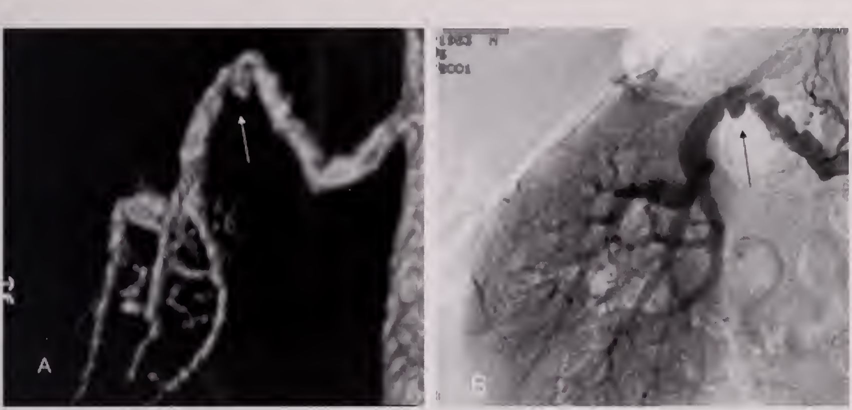

Fig. 4. (A) CE MRA, shows heading of the right renal artery in a patient with fibromuscular dysplasia (FMD). (B) Corresponding X-ray angiogram in the same patient.

cending aortic aneurysm to rule out a bicuspid aortic valve. Fast cine imaging allows visualization of jets produced in aortic regurgitation or stenosis. The aortic valve is also routinely imaged in type A aortic dissection. High-resolution black blood imaging of the coronary arteries is obtained for all type A aortic dissections as well as postoperative imaging of the ascending aorta.

Pretreatment Planning of Abdominal Aortic Aneurysms

In 1995, Parodi (24), in Argentina, first described endovascular repair of an abdominal aortic aneurysm. Imaging for preoperative aortic endograft design requires precise measurements. The consequences of small errors in graft sizing include endoleaks and graft migration. Currently, most centers employ both conventional angiography and CTA for pretreatment design of aortic endografts. Recently, some centers have shown good results in pretreatment planning of aortic endografts using either CTA or MRA alone (Figs. 5, 6) as well as facilitating the design of aortic endografts to be used. Measurements for endograft design include:

1. Aneurysm length measurements from the level of the lowest renal artery to the iliac bifurcation bilaterally. CE-MRA is acquired as a true 3D dataset with slices thin enough to approach true isotropic volumes. Similar data reconstruction algorithms can be applied to MRA which have been used for CTA.

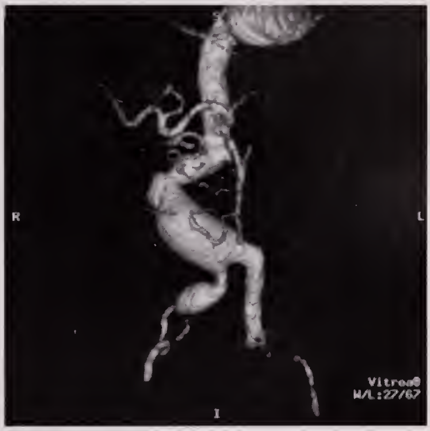

Fig. 5. Contrast-enhanced MRA of abdominal aortic aneurysm.

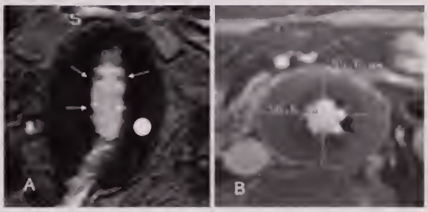

Fig. 6. (A) The arrows point to the artifact from the aortic stent-graft. (B) Measurement of AAA.

2. Accurate measurements of the diameter of the aorta at the level of the superior neck of the aneurysm and both common iliac arteries proximal to the iliac bifurcation are necessary. Precise measurements are crucial for the endovascular surgeon in endograft design. Diameter measurements should be performed in the vessel at a true orthogonal to the centerline of the vessel. This is best accomplished from reconstruction of MRA datasets.

3. Accurate visualization of the visceral vessels is important in determining stenosis of these vessels. This is important in planning endograft vs. open repair.

Post-aortic Stent-Graft Deployment for Abdominal Aortic Aneurysm

It is preferable to perform follow-up imaging with a noninvasive test such as MRA or CTA. Standard follow-up is recommended at one month and 6 months after stent placement. The majority of endoleaks are of Type 2, which may be caused by backfilling of the aneurysm sac by either the lumbar arteries or the inferior mesenteric artery (Fig. 6). Recent studies suggest that MRA is more sensitive for detecting Type 2 endoleaks than is CTA, and suggest that this is due to the increased sensitivity of MRI to contrast enhancement (25–28).

MR Artifacts of Endovascular Stents

1. Aortic stent-grafts (AneuRx, Talen) produce minimal artifact from the nitinol within the stent-graft. While this causes local distortion of the post-contrast images, vessel patency and endoleak can be visualized (Fig. 6).

2. The Wallstent, a cobalt-based alloy, causes major artifacts, obscuring visualization of vessel patency (Fig. 7).

3. Palmaz stent, a stainless steel stent, causes major artifacts, obscuring visualization of vessel patency.

4. Embolization coils cause major distortion artifacts, obscuring all adjacent organs, as well as vessel lumen patency (Fig. 8).

5. The platinum stent, a recently available stent for iliac or renal artery stenting, causes minimal artifact and allows for visualization of vessel patency (Fig. 9).

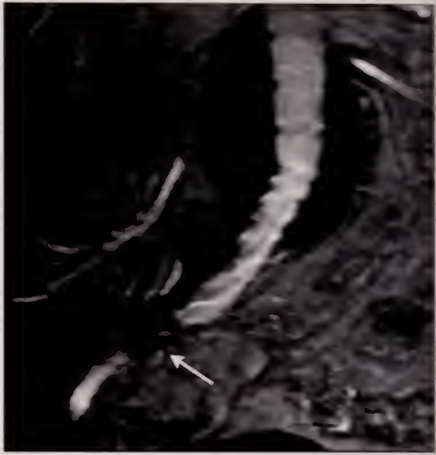

Fig. 7. AAA repaired with a stent-graft. The arrow points to the artifact from the right iliac artery Wallstent, which can be mistaken for an occlusion.

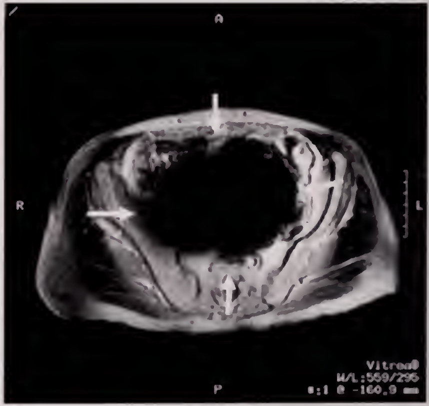

Fig. 8. Susceptibility artifact (arrows) from stainless steel embolization coils.

Research in the development of non-artifact-producing endovascular stents is ongoing (28, 29).

Pre- and Post-treatment Planning for Aortic Arch Aneurysms

Causes of aneurysmal dilatation of the aortic arch include atherosclerosis, trauma, arteri-

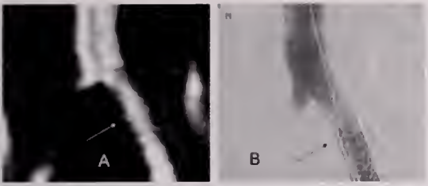

Fig. 9. **(A)** The arrow points to the minimal artifact which is caused by a platinum stent in the left iliac artery on MRA. **(B)** Digital subtraction angiogram of the same platinum stent in the left iliac artery (arrow).

tis, infection, connective tissue disease, aortic stenosis and congenital variants. Preoperative imaging of the aorta should include high-resolution imaging of the aortic wall, and cine imaging of the aortic valve and the aortic aneurysm. 3D CE-MRA of the aorta and 2D T1 weighted post-contrast images of the aorta are obtained. We have found 3D imaging useful in displaying the relationship of the aneurysm to the arch vessels in cases of complex anatomy (Fig. 10). Black blood imaging is useful for visualizing inflammation and thickening of the aortic wall. Cine imaging is useful for imaging the aortic valve and examining the distensibility of the aneurysm. Post-contrast 2D T1-weighted images are useful for visualizing thrombus and pseudoaneurysms. Measurements important for the endovascular surgeon are length of the aneurysm, diameter of the vessel before and after the aneurysm, and relationship of the aneurysm to the origin of the great vessels off the arch.

Pre- and Post-treatment of Aortic Dissection

Aortic dissection is the most common non-traumatic aortic pathologic condition (Fig. 11).

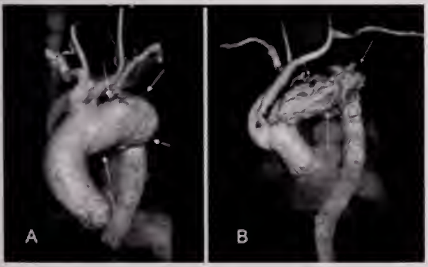

Fig. 10. **(A)** Arrows point to thoracic aortic aneurysm seen on CE-MRA. **(B)** Arrows point to artifact from aortic stent-graft repair of the thoracic aortic aneurysm in **(A)**.

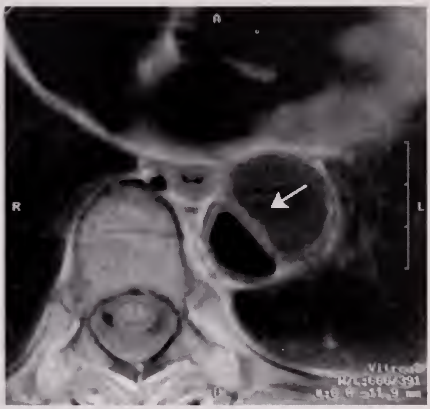

Fig. 11. Dissection in midthoracic aorta (arrow) using black blood MRA.

Imaging for aortic dissection must include identifying the origin of the intimal flap and its relationship to the arch vessels. In the case of a Stanford Type A left main dissection, imaging should include the aortic valve and the origin of the right and left coronary arteries. In the case of a Stanford Type B dissection, imaging should identify the origin of the visceral vessels from either the true or false lumens, and the distal extent of the flap. Our imaging protocol includes electrocardiographic-gated single-shot true fast imaging with steady-state precession (FISP) images through the entire aorta. 3D CE-MRA images can be obtained through the entire aorta to visualize vessel origins.

Pre- and Post-treatment of Takayasu's Arteritis

Takayasu's arteritis is the most common arteritis and usually occurs in young women of Asian descent. 3D CE-MRA imaging must include the entire aorta, including the arch vessels, in order to identify stenosis and aneurysmal dilatation. CE-MR imaging is useful in identifying aortic wall thickening, which we have found to be suggestive of active disease, and in assessing treatment response and flare-ups (Fig. 12).

Pre-and Post-treatment of Thoracic Aortic Aneurysms

High-resolution black blood or bright blood imaging can identify an intimal flap or pene-

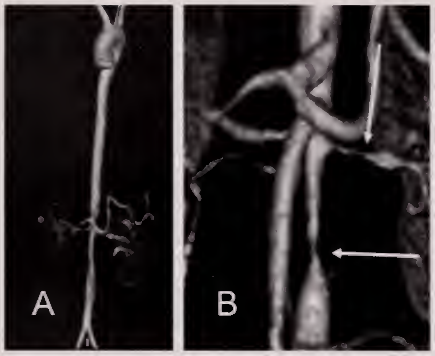

Fig. 12. **(A)** CE-MRA of the entire aorta in a patient with Takayasu's arteritis. **(B)** Arrows point to a high-grade stenosis in the left renal artery and the distal abdominal aorta.

trating ulcer. For proper endograft design, it is necessary to have accurate measurements of the aorta before and after the aneurysm as well as the length of the aneurysm. Imaging of the entire aorta is necessary to rule out abdominal aortic aneurysm. MRA of the iliac arteries should be included to aid the endovascular surgeon in pre-deployment approach of the stent-graft (30).

Conclusion

Contrast-enhanced MRA has made great advances over the last decade and is an increasingly useful and utilized examination for the noninvasive evaluation of vascular disease.

References

1. Korosec FR, Mistretta CA. MR angiography: basic principles and theory. Magn Reson Imaging Clin N Am 1998; 6(2):223–256.
2. Korosec FR, Frayne R, Grist TM, Mistretta CA. Time-resolved contrast-enhanced 3D MR angiography. Magn Reson Med 1996; 36(3):345–351.
3. Prince MR, Arnoldus C, Frisoli JK. Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. J Magn Reson Imaging 1996; 6(1):162–166.
4. Weinmann HJ, Brasch RC, Press WR, Wesbey GE. Characteristics of gadolinium-DTPA complex: a potential NMR contrast agent. AJR Am J Roentgenol 1984; 142(3):619–624.
5. Prince MR, Chenevert TL, Foo TK, et al. Contrast-enhanced abdominal MR angiography: optimization of imaging delay time by automating the detection of contrast material arrival in the aorta. Radiology 1997; 203(1):109–114.
6. Prince MR, Narasimham, DL, Stanley JC, et al. Breath-hold gadolinium-enhanced MR angiography of the abdominal aorta and its major branches. Radiology 1995; 197(3):785–792.
7. Maki JH, Prince MR, Londy FJ, Chenevert TL. The effects of time varying intravascular signal intensity and K-space acquisition order on three-dimensional MR angiography image quality. J Magn Reson Imaging 1996; 6(4):642–651.
8. Mezrich R. A perspective on K-space. Radiology 1995; 195(2):297–315.
9. Steffens JC, Link J, Gressner J, et al. Contrast-enhanced, K-space-centered, breath-hold MR angiography of the renal arteries and the abdominal aorta. J Magn Reson Imaging 1997; 7(4):617–622.
10. Wilman AH, Reiderer SJ, Huston J 3rd, et al. Arterial phase carotid and vertebral artery imaging in 3D contrast-enhanced MR angiography by combining fluoroscopic triggering with an elliptical centric acquisition order. Magn Reson Med 1998; 40(1):24–35.
11. Ho KY, Leiner T, de Haan MW, et al. Peripheral vascular tree stenoses: evaluation with moving-bed infusion-tracking MR angiography. Radiology 1998; 206(3):683–692.
12. Simonetti OP, Finn JP, White RD, et al. "Black blood" T2-weighted inversion-recovery MR imaging of the heart. Radiology 1996; 199(1):49–57.
13. Carr JC, Simonetti O, Bundy J, et al. Cine MR angiography of the heart with segmented true fast imaging with steady-state precession. Radiology 2001; 219(3):828–834.
14. Kuntz KM, Skillman SJ, Whittemore AD, Kent KC. Carotid endarterectomy in assymptomatic patients — is contrast angiography necessary? A morbidity analysis. J Vasc Surg 1995; 22(6):706–716.
15. Heiserman JE, Drayer BP, Fram EK, et al. Carotid artery stenosis: clinical efficacy of two-dimensional time-of-flight MR angiography. Radiology 1992; 182(3):761–768.
16. Litt AW, Eidelman EM, Pinto RS, et al. Diagnosis of carotid artery stenosis: comparison of 2DFT time-of-flight MR angiography with contrast angiography in 50 patients. AJNR Am J Neuroradiol 1991; 12(1):149–154.
17. Cosottini M, Pingitore A, Puglioli M, et al. Contrast-enhanced three-dimensional magnetic resonance angiography of atherosclerotic internal carotid stenosis as the noninvasive imaging modality in revascularization decision making. Stroke 2003; 34(3):660–664.
18. Levy RA, Prince MR. Arterial-phase three-dimensional contrast-enhanced MR angiography of the carotid arteries. AJR Am J Roentgenol 1996; 167(1):211–215.
19. Krinsky G, Rofsky N, Flyer M, et al. Gadolinium-enhanced three-dimensional MR angiography of acquired arch vessel disease. AJR Am J Roentgenol 1996; 167(4):981–987.
20. Postma CT, Joosten FB, Rosenbusch G, Thien T. Magnetic reonance angiography has a high reliability in the detection of renal artery stenosis. Am J Hypertens 1997; 10(9 Pt 1):957–963.
21. Rieumont MJ, Kaufman JJ, Geller SC, et al. Evaluation of renal artery stenosis with dynamic gadolinium enhanced MR angiography. AJR Am J Roentgenol 1997; 169(1):39–44.
22. Bakker J, Beek FJ, Beutler J, et al. Renal artery stenosis and accessory renal arteries: accuracy of detection and visualization with gadolinium-enhanced breath-hold MR angiography. Radiology 1998; 207(2):497–504.
23. Mittal T, Evans C, Perkins T, Wood AM. Renal arteriography using gadolinium enhanced 3D MR angiography — clinical experience with the technique, its limitations and pitfalls. Br J Radiol 2001; 74(882):495–502.
24. Parodi JC. Endovascular repair of abdominal aortic aneurysms and other arterial lesions. J Vasc Surg 1995; (21(4):549–555.

25. Haulon S, Lions C, McFadden EP, et al. Prospective evaluation of magnetic resonance imaging after endovascular treatment of infrarenal aortic aneurysms. Eur J Vasc Endovasc Surg 2001; 22(1):62–69.
26. Sawhney R, Kerlan RK, Wall SD, et al. Analysis of initial CT findings after endovascular repair of abdominal aortic aneurysm. Radiology 2001; 220(1):157–160.
27. Ludman CN, Yusuf SW, Whitaker SC, et al. Feasibility of using dynamic contrast-enhanced magnetic resonance angiography as the sole imaging modality prior to endovascular repair of abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2000; 19(5):524–530.
28. Maintz D, Kugel H, Schellhammer F, Landwehr P, et al. In vitro evaluation of intravascular stent artifacts in three-dimensional MR angiography. Invest Radiol 2001; 36(4):218–224.
29. Hilfiker PR, Quick HH, Debatin JF. Plain and covered stent-grafts: in vitro evaluation of characteristics at three-dimensional MR angiography. Radiology 1999; 211(3):693–697.
30. Snidow JJ, Johnson MS, Harris VJ, et al. Three-dimensional gadolinium-enhanced MR angiography for aortoiliac inflow assessment plus renal artery screening in a single breath hold. Radiology 1996; 198(3):725–732.

Devices and Techniques for Endovascular Surgery:

Catheters, Stents, Coated Stents, and Stented Grafts

Lev Pukin, M.D.

Abstract

Endovascular/minimally invasive surgery has undergone rapid innovation and growth. From crude, stiff, large-bore tubes that were used initially to evaluate vascular structures, some of the new catheters and wires are only a little bigger than the human hair, which permits their passage in vessels previously thought inaccessible. Closed arteries and veins now can be effectively traversed and blood flow restored by the use of balloons and metallic stents to maintain the integrity of the vascular lumen.

Key Words: Catheters, coated stents, endovascular devices, stents, stented grafts, endovascular surgery.

Catheters

Angiographic catheters can be divided into two broad categories, flush and selective. Whereas a flush catheter may be adequate to serve a therapeutic goal, a selective catheter is used for diagnosis. Both types of catheters come in a variety of shapes and sizes. Flush catheters are typically larger in caliber than selective catheters, which vary in diameter from 4 F to 6 F or greater (3 French = 1 mm) (Fig. 1).

The standard inner diameters of a diagnostic or flush catheter are 0.035 inch and 0.038 inch. Standard guide wires can be used. Construction and materials are important to consider when choosing the catheter. Materials used are teflon, nylon, polyurethane and polyethylene. Some have additional hydrophilic coating that makes the catheter slippery and easier to manipulate into an otherwise inaccessible vessel. To improve rotational torque, some catheters have a braided stainless steel mesh incorporated into their walls.

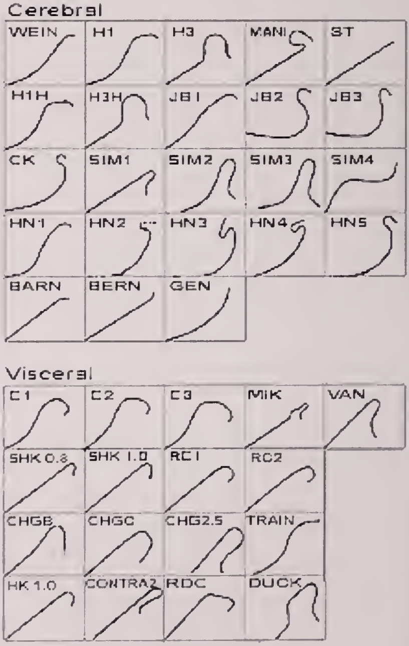

Fig. 1. A multitude of catheter shapes and sizes is available. Diagram courtesy of Boston Scientific, Natick, MA.

Address all correspondence to Lev Pukin, M.D., Assistant Professor of Radiology, Department of Radiology, Box 1234, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

To minimize the risk of stretching or fracture, catheters must have high tensile strength — yet still have a low coefficient of friction. Catheters must be able to resist high burst pressures associated with high injection rates, and still maintain their predetermined shape in order to pass through tortuous vessels. They must also have low thrombogenicity.

Catheters and their tips must be sufficiently radiopaque to aid fluoroscopic guidance. Since a large amount of contrast must be injected through the catheter into the vascular system in a relatively short period of time, a multi-hole catheter is used to avoid a dissection or rupture, which may occur following the use of an end-hole catheter.

Flush Catheters

Flush catheters come in various sizes and shapes. Some are straight, or shaped like a pigtail, a shepherd's crook, or a tennis-racket (Fig. 2). These can be easily manipulated into tortuous vessels, such as a contralateral iliac artery, and still provide excellent flow rate. But the end outcome is similar — high flow rate and no injury to the vessel, because contrast is delivered to a wide area. These catheters typically come in either 4 or 5 F sizes, but are available in a wider range of 3 to 8 F. To obtain accurate measurements within a vessel, some flush catheters come scored with centimeter markings that are radiopaque. A good example is a pigtail catheter that is routinely used to measure aneurysm length, and the distances from the adjacent vessels (Fig. 3)

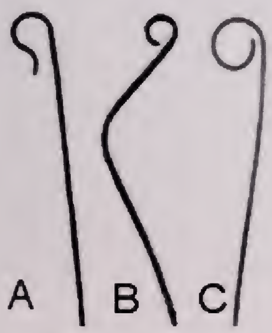

Fig. 2. Common flush catheters used in today's angiography. **(A)** Omniflush. **(B)** Grollman. **(C)** pigtail.

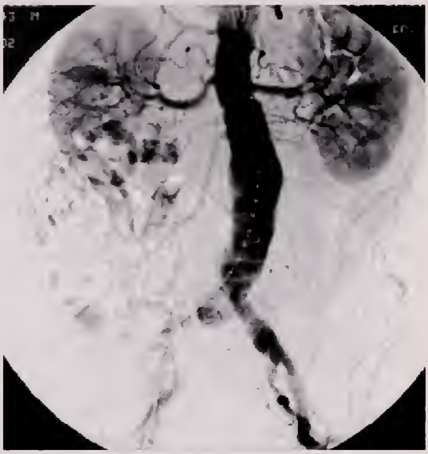

Fig. 3. AP view of the abdomen in a patient with an infrarenal abdominal aortic aneurysm. A marker pigtail catheter is positioned above the renal arteries. Following intravenous contrast injection, the abdominal aorta and the iliac system arteries are visualized.

Typically larger flow rates and stiffer catheters are helpful in pulmonary angiography, where a 6.5 F Grollman or Montefiore catheter can be used effectively, since the shapes make the manipulation through the heart chambers and into the pulmonary arteries and their branches much simpler.

Selective Catheters

Selective catheters come in many more shapes and sizes with preformed tips that can facilitate the selective catheterization of virtually any vessel. Choosing the correct one requires a consideration of the anatomy, vessel location and size, and possibly the disease involved.

Some catheters, such as the Berenstein catheter, are used more frequently than others (Fig. 4). This catheter is shaped like a small hockey stick and can be torqued in any direction. Similar catheters are available with varying curvatures, and lengths of tip.

When an artery or vein originates at an acute angle from its parent vessel, such as a left subclavian or left carotid artery, reverse curve catheters can be extremely helpful in engaging the lumen. Many such catheters exist. Simmons 1 and 2 have long been favorites (Fig. 5). Other catheters, such as the Mikaelsson and Sos-

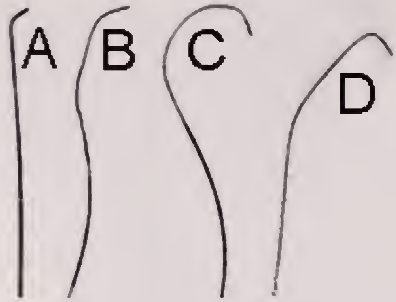

Fig. 4. Typical selective angiographic catheters: **(A)** Berenstein. **(B)** Headhunter. **(C)** Cobra. **(D)** spinal.

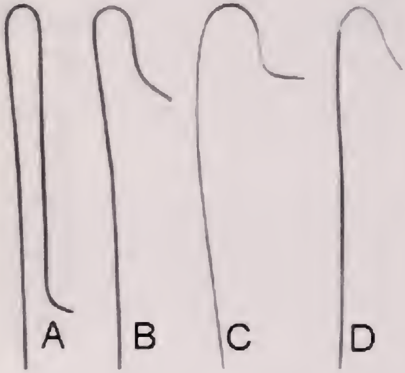

Fig. 5. Reverse curve catheters: **(A)** Bookstein. **(B)** Simmons. **(C)** Shetty. **(D)** Viscera hook.

selective, can provide quicker access to visceral or renal vessels. These reverse curve catheters, in which the tip is advanced into the vessel by withdrawing the catheter at the puncture site, must first be reformed into their original shape in the thoracic aorta prior to use.

Microcatheters

When a vessel is smaller than a conventional catheter, interventionalists resort to using microcatheters. These are typically 3 F or smaller and are placed coaxially through either a 4 or 5 F selective catheter. A number of factors influence the choice of a microcatheter. When a higher flow rate is required, a catheter with the largest possible inner lumen is preferred. Long and tortuous vessels require a more maneuverable catheter with hydrophilic coating that is trackable. The indications for preferring a particular catheter vary depending on whether its intended use is diagnostic or therapeutic, such as delivering chemotherapeutic agents into hepatic lesions, or embolizing them with various agents. The use of small catheters is helpful for embolizing bleeding vessels, vascular malformations, and small aneurysms.

Infusion Catheters

The infusion catheter is a variant of a flush catheter. The infusion catheter contains multiple side holes that are much smaller than one would find on a pigtail or similar catheter. A few varieties exist, but suffice it to say that the principle of delivering a thrombolytic agent into a clot is a constant feature of them all (Fig. 6).

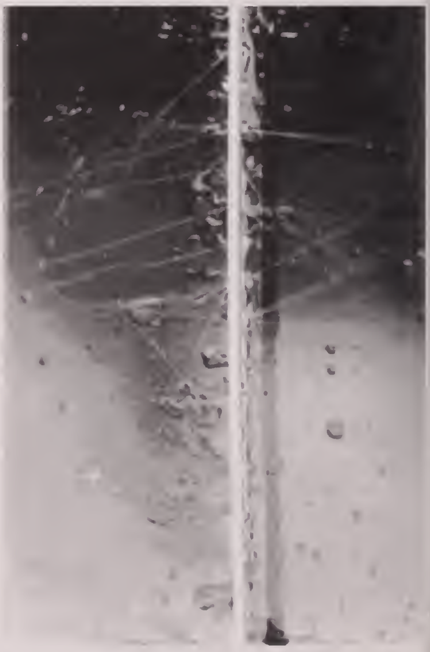

Fig. 6. An infusion catheter is designed to deliver medication over a predetermined distance with wide coverage. The side holes are numerous and much smaller than on a flush catheter.

Sheaths

The third type of catheter is one with a vascular sheath. They are used primarily to prevent oozing or hematoma formation at the access site, and when multiple catheter exchanges and a prolonged procedure time are expected. Most of these have a side-arm through which contrast can be injected, or fluids administered. These are also used to provide extra support and stabilize smaller, less sturdy catheters in place. An example would be a 60 cm long, 6 F sheath, positioned with the tip at the renal artery opening, with a smaller balloon catheter delivering a stent for the artery. Continuous contrast administration through the sheath aids in exact positioning of the balloon-stent combination (Fig. 7).

Angioplasty and Stents

The first true stent was developed by Palmaz in 1985; it remains the only FDA-approved device for peripheral arterial placement. Indications for the use of stents include suboptimal results after angioplasty (including recurrent or significant residual stenosis greater than 30% of lumen diameter, and a peak systolic arterial pressure gradient across the lesion of more than 10 mm Hg), complications of angioplasty or catheterization procedures (flow-limiting dissection or acute thrombosis), primary treatment of iliac artery occlusive disease, and primary treatment of ulcerative lesions in peripheral arteries with evidence of distal embolization and eccentric stenosis.

There are few contraindications to using a stent, such as a stenosis resistant to balloon angioplasty and arterial rupture after angioplasty. The second complication may be treated with a covered stent (a stent that has a material encircling the metal frame, thereby providing a contiguous coverage (Fig. 8). Relative contraindications include aneurysm within the vicinity of the stenotic segment and impaired pain sensation.

The intra- and post-procedural care of a patient undergoing stenting would include intravenous administration of 3000–5000 units of heparin immediately prior to stent deployment. A short course of anticoagulation (24 hours), with antiplatelet agents such as aspirin, or ticlopidine helps prevent immediate thrombosis of the device.

Immediately after stent placement, a thin layer of fibrin coats the luminal surface. Over several weeks, this layer of clot is gradually replaced by fibromuscular tissue. Reendothelialization of the stented vessel is thought to protect it from late thrombosis.

How the stents maintain vascular patency is a mechanism that is not completely understood. It is thought that wall stress imposed by the stent retards the process of intimal hyperplasia.

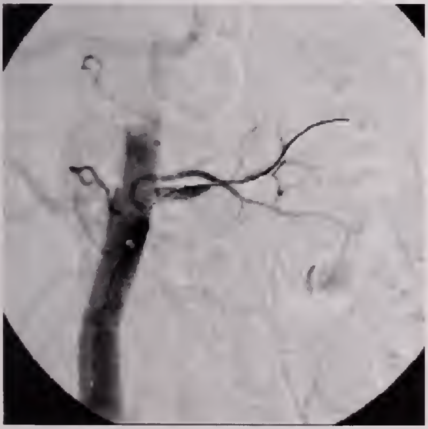
Fig. 7. A sheath tip is resting within the origin of the left renal artery; this facilitates precise placement of an over-the-wire stent. Additionally, contrast is being administered through the sheath, allowing for constant visualization of progress.

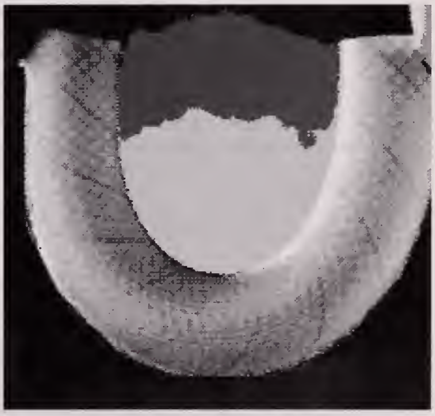
Fig. 8. Wallgraft. Self-expanding Wallstent with a fabric incorporated into the design, providing a solid tubular structure. Although this has FDA approval for use in tracheobronchial obstruction and fistulae, off-the-shelf uses include vascular and biliary work.

At the same time, dynamic thinning of the media is a constant feature of the stented arteries.

The most important properties of these devices are hoop strength, longitudinal flexibility, elastic and plastic deformation, length and composition. There are basically two stent designs: balloon-expandable and self-expandable.

Balloon-Expandable Stents

Balloon-expandable stents are premounted tightly onto a balloon-catheter, and are delivered into a lesion in a constrained form. They are deployed when the balloon is inflated. The benefit of using this type of stent is that it can be positioned precisely in a lesion. Although the approximate diameter is predetermined, the exact diameter of the expanded stent depends on what diameter balloon is used for the inflation. These stents retain the diameter imposed by the angioplasty balloon, but also are compressed externally.

The Palmaz stent (Cordis/Johnson and Johnson, Warren, NJ) is a prototype of a balloon-expandable stent. It is rigid and made of stainless steel. Many sizes are available, varying in length from 8 – 75 mm, and in diameter from 3 – 12 mm. The stent shortens minimally as the balloon expands. This allows for a precise positioning. Because this type of stent has only minimal longitudinal flexibility and is subject to permanent plastic deformation, it should be placed into a relatively straight vascular segment, such as a renal artery or superior mesenteric artery, and not at sites such as dialysis grafts, femoral or other joints, or thoracic outlet veins, where an extrinsic force could crush it.

One example of a newer balloon-expandable stent is a Genesis transhepatic biliary stent. It represents the next generation of the Palmaz type, having much better trackability and higher radial strength. It comes premounted on a smaller profile balloon catheter, and is 6 F guide catheter compatible (Figs. 9 – 12).

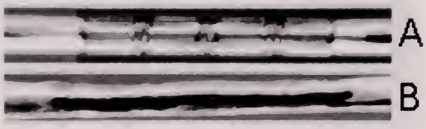

Fig. 9. (**A**) Genesis stent. (**B**) After removal of the stent, the balloon appears to have been nearly flush with the stent.

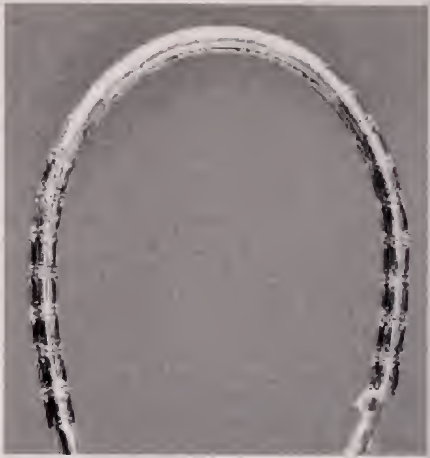

Fig. 10. A long Genesis stent demonstrates marked flexibility, compared to older generation of similar technology.

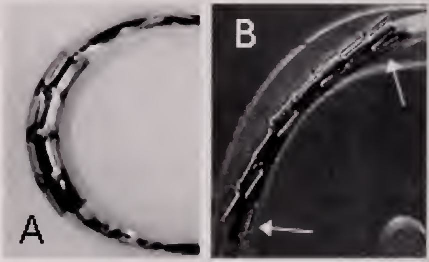

Fig. 11. Newer technology allows for a more flexible stent design. (**A**) Stent retains its crimped shape, whereas in **B**, stent demonstrates flaring of the tips (arrows).

Self-Expanding Stents

Self-expanding stents are held in place within a catheter, and are deployed by removing the constraining sheath, exposing the stent to the vessel. The final diameter is predetermined, but is also a function of the elastic recoil of the vessel wall.

A Wallstent (Boston Scientific, Natick, MA) is a prototype of a self-expanding stent. It is composed of stainless steel filaments woven in a cross-hatched pattern. It also comes in many sizes, with the diameter ranging from 5 – 24 mm, and a fully deployed length of

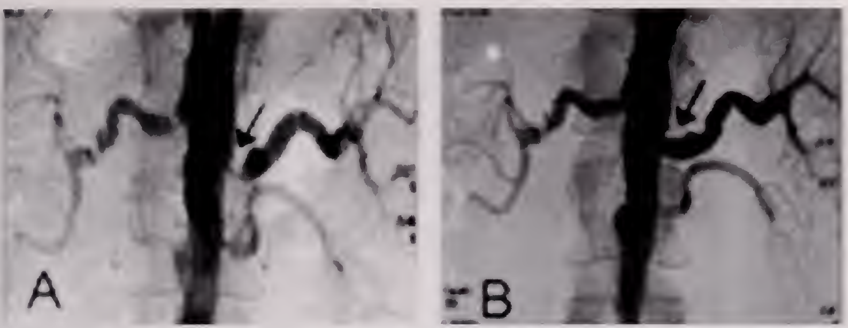

Fig. 12. Before **(A)** and after **(B)** bilateral renal artery stenting with Genesis 6 mm × 15 mm stents to restore luminal patency (arrows).

20–94 mm. Because the compressed length of the stent is significantly longer than its expanded length, placement is much less precise than with the balloon-expandable stents. These stents have almost no plastic deformity but considerable elastic deformity and longitudinal flexibility. Because of these characteristics, maneuverability and delivery of the stent catheter through tortuous vessels and tight curves is particularly easy (Fig. 13). Newer technologies and materials make it possible to manufacture stents that have higher tensile strength, increased visibility, smaller profile of the delivery device, and decreased thrombogenicity.

The new self-expandable catheters include SMART (Shape Memory Alloy Recoverable Technology (Fig. 14) and Precise, an 0.018" system (Cordis, Johnson and Johnson company, New Brunswick, NJ). These stents are made from nitinol, a polymer of nickel and titanium, giving them much more flexibility at room temperature, and a rigid, predetermined shape at body temperature. An excellent improvement over their competitors is their minimal shortening, allowing for much more accurate positioning.

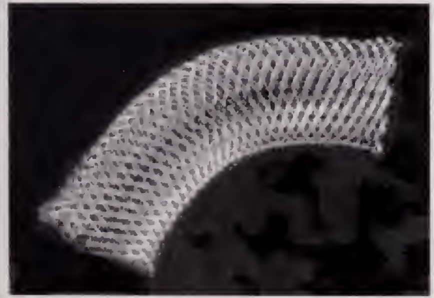

Fig. 13. Wallstent. Diagram courtesy of Boston Scientific, Natick, MA.

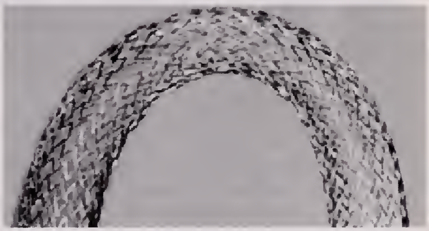

Fig. 14. SMART stent.

The use of newer materials and manufacturing technologies allows for a better surveillance of the stented vascular structures. In the past, artifacts from the implantable metal devices such as stents produced marked artifact on imaging studies, such as CT and MRI. However, today, non-invasive follow-up of patients can be performed with little or no difficulty in assessing the luminal patency and/or stenosis (Fig. 15).

Stents, unfortunately, are not without long-term problems. Their widespread use has led to an appreciation of the occurrence of in-stent restenosis (ISR). This occurs primarily as a result of proliferating smooth muscle cells and extracellular matrix. ISR is more apt to occur in women, in patients with diabetes, and in cases of long lesions with significant total plaque burden after stenting (assessed by intravascular ultrasound), small vessel diameter, and with the use of multiple stents and certain types of stent.

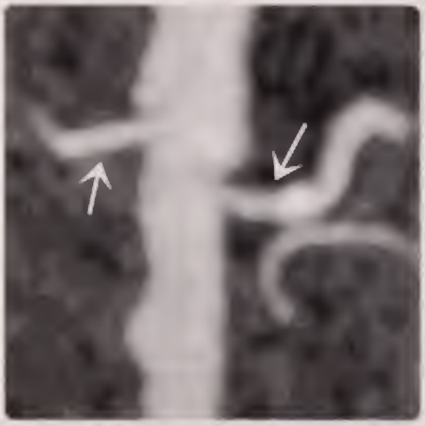

Fig. 15. MRA image of bilateral renal arteries following placement of platinum stents (arrows).

Mechanical strategies and systemic drugs have been employed to inhibit the neointimal hyperplasia. However, the most promising modality has been the recent use of drug-eluting stents (1).

A distinction must be made between drug-eluting stents and simple coated ones. Simple coated stents are covered either with a polymer (phosphorylcholine silicon carbide) or with a drug directly applied to the metal (e.g., heparin-coated stents and paclitaxel-coated stents). These are primarily used to decrease the thrombogenicity of the metal. On the other hand, drug-eluting stents have both a polymer and a drug spread over the metal, allowing for slow release of the drug directly into the adjacent tissue, targeting the process of neointimal hyperplasia. Numerous combinations of coatings have been studied. Some have proven to actually increase the rate of restenosis or to be proinflammatory (2).

Recent studies using drug-eluting stents containing rapamycin, an immunosuppressive agent, and paclitaxel have demonstrated potent cell cycle inhibitory effects. Both drugs inhibit cellular proliferation by different mechanisms (1).

Experience with the rapamycin eluting stent was recently reported in a 45-patient registry (1). At one year, there was no angiographic or intravascular ultrasound (IVUS) restenosis, nor were there stent-related adverse events. The results of the first randomized double-blind study (RAVEL) using the slow release combination of rapamycin, were reported at the European Society of Cardiology in September 2001. In this trial, for the first time in the history of vascular intervention, the incidence of in-stent-restenosis (ISR) in the treatment arm was 0% compared to 26% in the control group (2).

Paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, NJ) is a microtubule-stabilizing compound with potent antitumor activity. Results similar to that of rapamycin have been found. ASPECT (Asian Paclitaxel Eluting Stent Clinical Trial) demonstrated a restenosis rate of 4% vs. 27% in a control group. ELUTES, a European dose-ranging study presented at the American Heart Association 74th Scientific Sessions, showed comparable results of ISR of 3% vs. 21% in bare metal group. TAXUS I trial used a polymer-based paclitaxel eluting NIR stent (Boston Scientific, Natick, MA), with a 6-month restenosis rate of 0% compared to 11% in the control group (2). More studies enrolling larger groups of patients are needed to substantiate these encouraging results.

Although rapamycin and paclitaxel have been most studied, other combinations are also being investigated. These include tacrolimus, dexamethasone, batimastat, rapamycin analogs, phosphorylcholine, liposomal encapsulated PGE-1, and c-myc antisense oligonucleotides (2). Additionally, prospective experimental therapies include creating molecules of DNA and RNA to inhibit specific genes involved in the ISR. Gene transfer techniques would be employed to introduce these agents to the desired location, to inhibit neointimal proliferation.

Conclusion

Long-term outcomes of these new techniques are yet to be reported. However, new advances in the technology as well as the technique are very promising. Additionally, patients who were considered inoperable just a few years ago now have the opportunity to reduce their existing disability and risk, and enhance the quality of their life.

References

1. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation 2001; 104:2007–2011.
2. Garza L, Aude YW, Saucedo JF. Can we prevent in-stent restenosis? Curr Opin Cardiol 2002; 17(5):518–525.

Endovascular Therapy for Atherosclerotic Occlusion and Stenosis from the Infrarenal Aorta to the Infrapopliteal Arteries

F. SCOTT NOWAKOWSKI, M.D.[1], AND HANK J. FREEMAN, M.D.[2]

Abstract

Aortoiliac and peripheral vascular disease that cannot be treated medically is generally treated by vascular surgeons and/or interventional radiologists. Advances in technology have allowed endovascular therapy to become a therapeutic option for atherosclerotic disease from the aorta to the femoropopliteal region. Distal peripheral disease is still approached surgically; however, further technological advances may lead to a more active role for endovascular therapy at this level.

Key Words: Peripheral vascular disease, infrarenal aorta, iliac arteries, femoral arteries, popliteal arteries, minimally invasive, vascular surgery, endovascular therapy.

Introduction

ATHEROSCLEROSIS is the most common disease involving the infrarenal aorta, pelvic and lower extremity vasculature. Many of its consequences can be treated by vascular surgeons and interventional radiologists. Peripheral vascular disease (PVD) affects 2–3% of males and 1% of females over the age of 60 (1). Risk factors for this disease include smoking, diabetes, hyperlipidemia, obesity, male sex, and advancing age. Symptomatology of PVD includes intermittent claudication, pain at rest, and non-healing ulcers of one or both of the lower extremities. The initial work-up for patients with suspected PVD entails a detailed history, including symptomatology, prior surgeries, other medical conditions, and social history which may be relevant to the disease. Physical findings may include decreased femoral or distal pulses, ulcerations, cool extremities and skin changes. The results of laboratory tests of blood and urine may reveal contributing etiologies (e.g., hyperlipidemia) as well as other problems, which must be excluded when preparing for possible surgical or endovascular intervention.

Noninvasive testing (e.g., for ankle-brachial pressure indices [ABIs]) is an important next step in the evaluation of PVD. Claudication can be seen in patients with ABIs of less than 0.92. Values less than 0.5 are seen in patients with severe disease and pain at rest; tissue loss is typically noted with values of less than 0.3. Poor prognosis for healing of lower extremity ulcerations is noted when the blood pressure in a lower extremity is 30 mm Hg less than that measured in the arm on the same side of the body (2). Computed tomographic arteriography (CTA) and magnetic resonance arteriography (MRA) are two noninvasive modalities that are growing in popularity as diagnostic tools for aortoiliac disease and PVD (3, 4). These modalities have come close to rivaling arteriography, the gold standard in the assessment of aortoiliac disease. Despite a sensitivity and specificity of MRA approaching 95%, there remains a reluctance to accept this examination because certain information (such as direction of flow beyond occluded segments and post-processing artifacts) may not be acquired (5).

Once it has been established that PVD is responsible for the patient's symptoms, arteriography can be obtained for diagnostic purposes, preoperative planning, and possible interven-

---

[1]Assistant Professor of Radiology and [2]Diagnostic Radiology Resident, Department of Radiology, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to F. Scott Nowakowski, M.D., Department of Radiology, Box 1234, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

tion. Evaluation of the patient's laboratory values, including blood urea nitrogen (BUN)/creatinine, coagulation studies and platelet count, are essential. Patient preparation for the angiographic procedure includes adequate hydration when possible and the administration of renal-protective agents such as acetylcysteine and fenoldopam to patients with decreased renal function (6). Also, alternative contrast agents such as the low osmolar contrast, CO_2, or gadolinium can be utilized to decrease the nephrotoxicity which may be related to the use of high osmolar contrast agents. Patients with coagulopathies or low platelet count can be given fresh frozen plasma or pooled platelets. If there is a history of adverse reaction to contrast agents, steroids can be administered prior to the procedure.

The interventional radiologist should obtain a focused history, perform a physical examination, and then review all prior diagnostic studies and physical findings with the referring clinician and/or vascular surgeon. The site of the disease should be determined with certainty, since this will guide the approach to arteriography. Informed consent is obtained from the patient for both a diagnostic procedure and possible intervention (percutaneous transluminal balloon angioplasty, stent placement, thrombolytic therapy). Whereas in the past the intervention was often performed independently of the diagnostic procedure, most interventions are now performed at the same sitting.

Vascular access for the diagnostic procedure is usually obtained via the common femoral artery, using either the Seldinger technique or a single-wall needle. The puncture site is usually determined based on prior knowledge of disease or physical findings (e.g., stronger common femoral artery pulse). Occasionally, when femoral access is not feasible (e.g., bilateral common femoral artery occlusions), a left high brachial artery approach can be used. Rarely, a translumbar route to the aorta is utilized for a diagnostic study. Diagnostically, it is important for the interventionalist to perform a study yielding as much information as possible, while being mindful of the contrast burden being administered to the patient. This includes obtaining multiple projections (anteroposterior, lateral and bilateral 30 degree obliques of the pelvic vasculature) and pressure measurements across questionable lesions to assess for hemodynamic significance (7). Administration of vasodilators intra-arterially (25 mg talazoline, 100–200 μg nitroglycerine or 30 mg papavarine) can be performed in an attempt to better define the hemodynamic significance of an equivocal lesion. Usually a gradient greater than 5–10 mm Hg at rest and greater than 15–20 mm Hg following administration of one of the aforementioned drugs is considered hemodynamically significant. It must be noted, however, that pressure gradients proximal to an occlusion can be surprisingly low or near normal (i.e., measuring across a common iliac stenosis proximal to a superficial femoral artery occlusion). Also, reactive hyperemia induced by these drugs can be used to facilitate the visualization of diseased trifurcation vessels below the calf.

Focal Aortic Stenosis / Occlusion

Focal aortic stenosis / occlusion is a relatively uncommon form of peripheral vascular disease seen predominantly in younger patients who smoke (8) (Figs. 1, 2). The characteristic lesions may produce claudication and distal ischemic symptoms but often manifest as Leriche syndrome (infrarenal aortic occlusion), which can produce the triad of buttock claudication, impotence and absent femoral pulses. In the past these lesions were treated primarily via surgery, but advances in endovascular techniques have made percutaneous transluminal angioplasty (PTA), with or without subsequent stent placement, the current treatment of choice.

Technically, once the appropriate common femoral artery has been accessed and a vascular sheath placed, the lesion should be carefully traversed with an atraumatic floppy-tipped wire to avoid subintimal passage. A directional catheter can be used to negotiate difficult lesions. Although prior to PTA, thrombolytics were commonly used for aortic and iliac occlusions, these agents are much less likely to be used now, unless there is frank evidence of fresh thrombus (9). Once across the lesion, heparin (3000–7000 U IV) is administered by some physicians, depending on factors such as slow flow associated with marked stenosis. A marking pigtail catheter can then be passed over the guidewire and a diagnostic aortogram can be performed to discern the aortic diameter and the appropriate choice of balloon catheter. The aorta can be dilated to a diameter which does not exceed that measured just proximal or distal to the lesion. Aortic stretching beyond its normal size during angioplasty is thereby minimized. Depending upon the size of the lesion, a single PTA catheter, or two PTA catheters with the second introduced via a contralateral common femoral artery puncture, can be utilized to

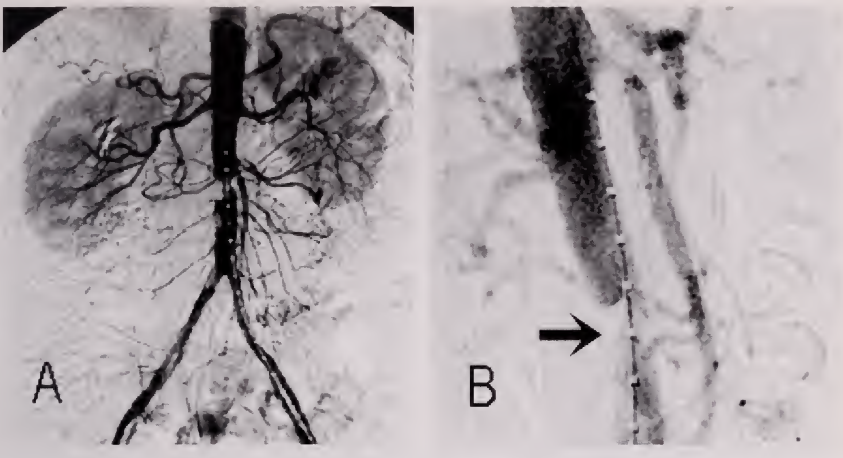

Fig. 1. (**A**) Tight focal abdominal aortic stenosis in patient with Leriche syndrome. A systolic pressure gradient of 67 mm Hg was present. (**B**) Lateral aortogram (arrow) reveals the extent of the disease in the AP dimension.

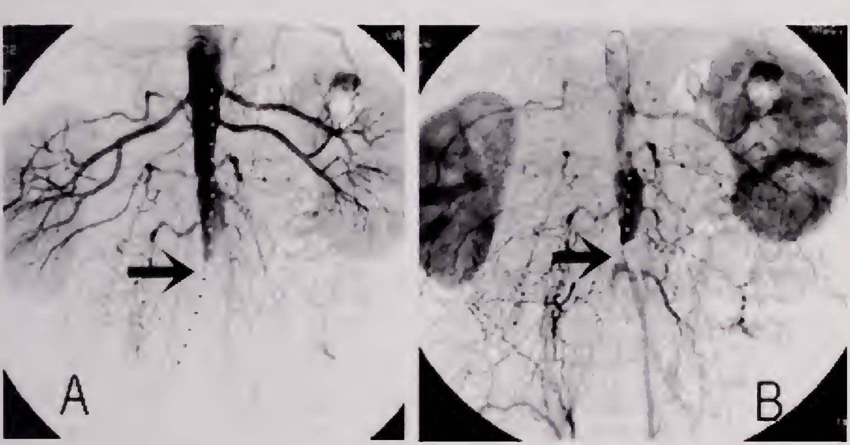

Fig. 2. (**A**) Early phase of abdominal aortogram revealing tight focal stenosis of the distal abdominal aorta (arrow) in patient with Leriche syndrome. (**B**) Later phase of aortogram reveals tight focal aortic stenosis with patent common iliac arteries bilaterally filling predominantly via collateral circulation (arrow).

dilate the aorta. After follow-up aortography to assess aortic patency and exclude residual stenosis or flow-limiting dissection, pressures can be measured across the newly dilated lesion to assess for hemodynamically significant gradients. Failure of PTA is an indication for aortic stent placement.

Although primary aortic stenting has been advocated as an alternative to surgery for focal aortic disease (10) (Figs. 3, 4), studies comparing PTA with aortic stenting (generally balloon-expandable stents) have yielded conflicting results (11,12). Recently, self-expanding stents (Wallstent [Boston Scientific, Watertown, MA], SMARTstent [Cordis Corporation, Miami, FL]) have been utilized to treat these lesions. Long-term results are not yet available to assess the efficacy of this technique, although anecdotal reports are encouraging.

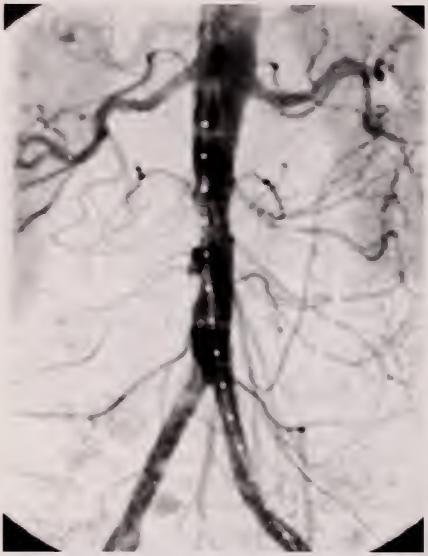

Fig. 3. Abdominal aortogram following placement of self-expanding stent in same patient as in Fig. 1. Final systolic pressure gradient was less than 5 mm Hg.

The initial approach to stenting is similar to that for PTA. Once the appropriate-size stent is chosen, road-mapping can be employed for exact stent placement. The lesion is commonly pre-dilated with an 8 – 10 mm balloon catheter. For distal aortic lesions which may or may not extend into the iliac system, bilateral stents extending into the common iliac arteries can be deployed. Balloon-expandable stents are deployed via the "kissing balloon / stent" technique, in which simultaneous deployment is performed (Fig. 5). Self-expanding stents can be deployed simultaneously or sequentially (with the contralateral catheter utilized to inject contrast, to ensure exact initial stent placement). Extreme caution is essential to ensure that the initial stent is not dislodged upon exchange and positioning of the second stent. Following treatment of these lesions, either by PTA or stent, physical findings such as diminished peripheral pulses or non-healing ulcers should show marked improvement. For patients whose physical examination results worsen or who develop increased lower extremity symptomatology, additional images are imperative to assess for possible dissection and thromboembolism prior to removal of the vascular sheaths.

Aortoiliac Stenosis / Occlusion

Aortoiliac atherosclerotic disease resulting in hemodynamically significant stenoses and/or occlusion are readily treated via endovascular therapy. Recent studies have indicated the advantage of endovascular therapy over surgery for certain types of lesions (13). PTA is the treatment of choice for a single stenosis of the common iliac artery (CIA) or external iliac artery (EIA), either unilateral or bilateral, of less than 3 cm in length. Surgery, when compared to PTA, is recommended for diffuse disease involving the CIA, EIA or common femoral artery (CFA), bilateral EIA occlusions, unilateral occlusion involving both the CIA and EIA, diffuse disease involving the aorta and bilateral iliac arteries, or iliac stenoses in patients with abdominal aortic aneurysm. According to the Trans Atlantic Inter-Society Consensus (TASC), definitive recommendations must await more evidence regarding the outcomes of treatment of lesions such as unilateral and bilateral CIA occlusions, unilateral EIA occlusion (or stenosis extending into the CFA), single stenoses 3 – 10 cm in length (not extending into the CFA), two stenoses each less than 5 cm long (not extending into the CFA), and bilateral stenoses 5 – 10 cm long (not extending into the CFA) (13). The Cardiovascular and Interventional Radiological Society of Europe (CIRSE) has noted that before firm recommendations can be made on the aforementioned "gray area" lesions, more evidence must be obtained (13), even though these lesions are more commonly being treated with endovascular therapy and endovascular stents with reasonable technical success.

Recent studies have displayed the significance of elastic recoil in the iliac arteries following PTA of stenoses, suggesting that vascular stents, by limiting elastic recoil, are an important tool in maintaining patency following endovascular procedures (14). TASC agrees that for some lesions that were previously in the gray area of treatment options and for selected patients for whom surgery was previously thought to be the treatment of choice, vascular stent placement can improve immediate hemodynamic results. Kandarpa et al. (15), expanding on that conclusion, consider endovascular therapy to be the treatment of choice for a single stenosis up to 10 cm in length, and for two stenoses each less than 5 cm in length for lesions of the CIA or EIA (not extending into the CFA), and for unilateral occlusions of the CIA. Vascular stents have also been successfully utilized in treat-

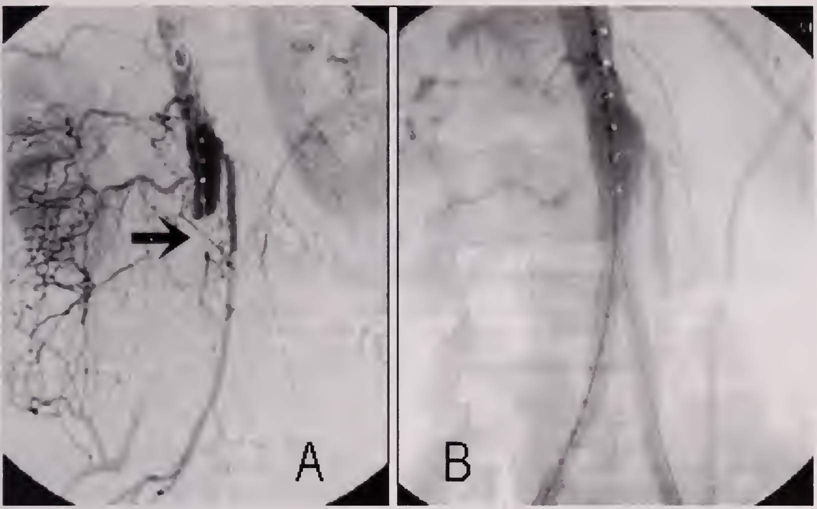

Fig. 4. (A) Early phase of oblique abdominal aortogram in same patient as in Fig. 2 prior to stent deployment, revealing tight focal aortic stenosis (arrow) with extensive collateral flow reconstituting the iliac vessels. **(B)** Oblique abdominal aortogram revealing widely patent abdominal aorta following deployment of self-expanding stents into the iliofemoral system. Final pressure gradient from the aorta to the external iliac arteries was less than 10 mm Hg. Common femoral artery pulses, barely palpable prior to the procedure, were 2+ following stent placement.

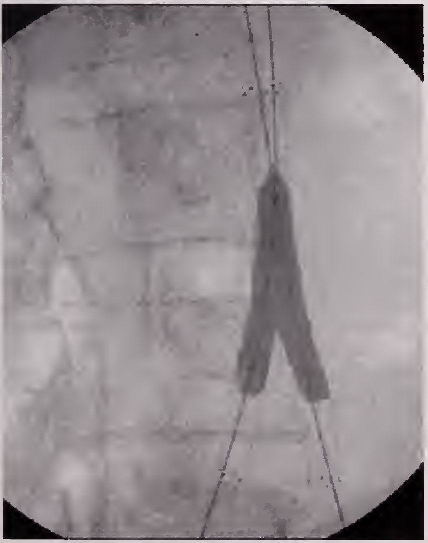

Fig. 5. "Kissing balloon" technique reducing the residual waist in two previously placed self-expanding stents (same patient as in Fig. 4).

ing PTA-induced flow-limiting dissections, thus making endovascular therapy more attractive for lesions for which dissection was a concern.

Vascular stents have also altered thinking regarding the approach to chronic aortoiliac occlusions (Fig. 6). Surgery had always been the mainstay in the past, since PTA of these lesions generally yielded poor results. Studies comparing stents to PTA, however, have shown the benefits of stenting these lesions (16, 17). Although results from recent studies such as the Dutch Iliac Stent Trial reveal the hemodymamic and clinical success rates of primary stent placement, compared to primary angioplasty followed by selective stent placement, to be nearly identical at two years, mild lesions were predominantly treated in this study (18). It is thought unlikely that more severe lesions would respond in a similar fashion. Whereas low-dose thrombolysis of occluded iliac lesions was once utilized prior to stenting, recent studies indicate that primary stent placement can be safe and efficacious without prior thrombolytic therapy (18) and should be the treatment of choice for chronic iliac artery occlusion.

The technical approaches for aortoiliac PTA and stenting are similar to those for focal aortic

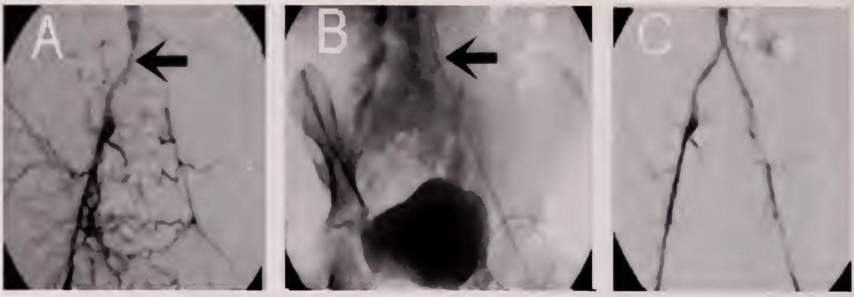

Fig. 6. **(A)** Pelvic arteriography revealing left common iliac occlusion with reconstitution of the external iliac artery via collateral circulation (arrow). **(B)** Oblique view of the pelvis showing the self-expanding stent successfully deployed across the common iliac occlusion following careful manipulation across the lesion (arrow). **(C)** Final pelvic arteriogram reveals widely patent left common iliac artery following self-expanding stent deployment.

disease. The initial approach to the lesion (ipsilateral or contralateral) depends on prior knowledge of the lesion (via physical examination, symptoms, ABI, noninvasive imaging) and physician preference. Common and external iliac disease can be approached via either an ipsilateral or a contralateral approach. If the angle of the aortic bifurcation is not too acute, a contralateral approach is sometimes preferred, since treating potential downstream complications such as embolism is not feasible from an ipsilateral approach. Also, thrombolytic therapy for *in situ* thrombosis after PTA or stent deployment may worsen bleeding complications at the downstream puncture site (19). An "up and over" sheath can be placed; it conveys the additional convenience of the capability of "puffing" contrast through the side port of the sheath for exact balloon or stent placement and the ability to do post-procedure runs immediately, without employing catheter exchange. An ipsilateral retrograde approach is still the preferred access for many physicians, since it provides a direct, "straight-line" approach to the lesion. An ipsilateral approach is also utilized when an acute aortic bifurcation is present.

Balloon-expandable stents have traditionally been the preferred choice in stenting of aortoiliac disease. Most studies in the literature have involved this type of stent. More recently, however, self-expanding stents have been utilized in the aortoiliac system with a great deal of success (17, 20). These stents are particularly useful in markedly tortuous iliac vessels and can conform to various vessel dimensions and diameters within the same patient, especially when particularly long lesions are stented. Following deployment, PTA of residual stenoses secondary to extrinsic compression upon the stent can be performed. It is important to stay within the confines of the stent when performing PTA, since angioplasty of normal vessel beyond the stent may lead to intimal hyperplasia just proximal or distal to the stent. More studies on self-expanding stents need to be performed to ascertain their long-term efficacy in aortoiliac occlusive disease.

Femoropopliteal Disease

There are a number of factors that distinguish atherosclerotic disease of the femoropopliteal system from isolated aortoiliac disease. Occlusions tend to be more common than stenoses. Also, patients with femoropopliteal disease are more likely to have comorbidities such as coronary artery disease (21). Thus, when feasible, endovascular therapy would be preferred to surgery for these patients, who are at relatively high risk. Also, preservation of autologous vein, usually used in lower extremity bypass grafts for possible future coronary artery bypass grafting, is a potential benefit of performing endovascular therapy.

Balloon angioplasty has been the preferred endovascular treatment for solitary stenoses of the superficial femoral artery (SFA) less than 10 cm in length, tandem lesions less than 3 cm long, and lesions just proximal to planned distal bypass procedures (not involving the SFA origin or extending into the popliteal artery). PTA has also been shown to be safe and effective for SFA occlusions less than 3 cm in length. The addition of stents for the aforementioned lesions as well as solitary SFA occlusions less than 10 cm and tandem occlusions less than 3 cm in length improves initial success and patency rates, but has been shown to confer no benefits in long-term patency (Fig. 7). It has therefore been recommended that stent placement be reserved for PTA failures secondary to elastic recoil or flow-limiting dissection, or for limb salvage (13, 22).

For lesions below the inguinal ligament, either a contralateral retrograde or an ipsilateral antegrade access is utilized, again based on prior knowledge of the lesions and physician preference. A contralateral approach is sometimes preferred, to avoid any potential complications to inflow such as dissection or hematoma formation, which may occur from an ipsilateral antegrade puncture. Left high brachial approach and ipsilateral retrograde popliteal approach have been described, but are rarely used. The general principles for PTA and stenting mentioned in previous sections also apply to the femoropopliteal region. Extra care must be employed in this region, as passage of wires into the infrapopliteal region may initiate spasm and subsequent thrombosis in these sensitive vessels. Multiple lesions should be approached in a proximal-to-distal fashion.

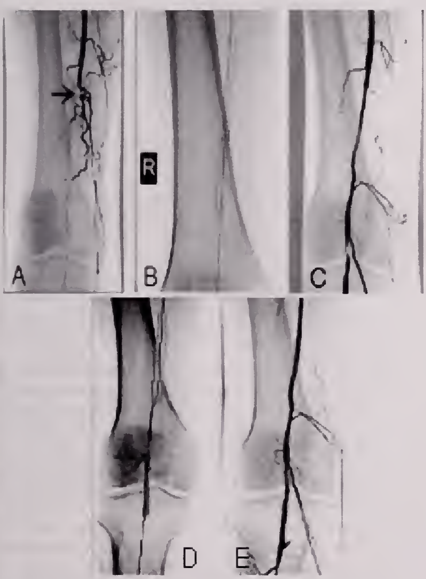

Fig. 7. (**A**) Early phase of arteriogram revealing distal superficial femoral artery (SFA) occlusion (arrow) with reconstitution of the distal SFA / proximal popliteal artery via collateral circulation. (**B**) Self-expanding stent was successfully deployed across the superficial femoral artery occlusion. (**C**) Arteriogram reveals widely patent superficial femoral artery following stent deployment. A previously noted popliteal artery stenosis is more apparent on this study. (**D**) Balloon angioplasty of the popliteal artery stenosis seen in C is performed following deployment of the more proximal SFA stent. (**E**) Final arteriogram reveals widely patent distal SFA and popliteal artery following stent deployment and PTA, respectively.

The use of other techniques for femoropopliteal revascularization have had mixed results. The use of atherectomy devices and polytetrafluoroethylene (PTFE)-covered stent-grafts has yielded disappointing patency rates (23, 24). Subintimal angioplasty has revealed successful results but has failed to gain popularity. Self-expanding nitinol (nickel titanium polymer) coil stents have been shown to be safe and effective in PTA failures and are of particular use in the distal SFA and popliteal artery because of their unique longitudinal flexibility (25). Laser-assisted angioplasty has been successfully utilized in the recanalization of infrainguinal occlusions averaging approximately 20 cm in length (26). The results following the of drug-eluting stents seem to encourage the most optimism, as preliminary studies have shown a six-month restenosis rate of 0% when using these stents to treat obstructive SFA disease (27). However, more evidence must be obtained regarding the efficacy of these modalities in the treatment of infrainguinal disease.

Infrapopliteal Disease

Patients with infrapopliteal disease, like those with femoropopliteal disease, tend to have comorbidities such as hypertension, cardiac disease, chronic renal insufficiency and cerebral vascular disease. A majority of these patients are diabetics. The role of endovascular therapy in the treatment of infrapopliteal disease has traditionally been limited. Recent studies, however, have shown the benefit of infrapopliteal PTA for limb salvage in critical limb ischemia (28).

Technologic advances such as floppy-tipped steerable guidewires (0.014–0.018 inch) and low-profile balloons (2–4 mm) have increased the efficacy of infrapopliteal procedures; the resulting limb salvage rates are now comparable to rates with surgical techniques, for selected patients. The use of intra-arterial nitroglycerine (and often the addition of sublingual nifedipine) in these vessels, which are particularly sensitive to spasm, is essential. An intravenous or intra-arterial bolus of heparin, 5000–7000 U, is generally administered. Techniques such as passing a safety wire down the adjacent vessel when performing PTA at a branch point can help avoid occlusions of nonstenosed vessels by dissection or displacement of intimal plaque. Technical success rates, (with "success" defined as successful balloon angioplasty or stent deployment), have been high, with the greatest clinical results noted when straight-line blood flow to the foot has been restored (29).

Summary

Endovascular therapy has emerged as a primary modality in the approach to aortoiliac and peripheral vascular disease. Technologic advances have allowed endovascular therapy to become the treatment of choice for most infrarenal aortic, iliofemoral, and femoropopliteal stenoses and occlusions. The role of balloon angioplasty in the infrapopliteal region is still limited, but it is being used more frequently as knowledge of drug therapy and improved catheter, wire and balloon systems increases. Further clinical tests on alternative endovascular modalities need to be performed to assess their efficacy in the treatment of peripheral vascular disease.

References

1. Genton E, Clagett GP, Salzman EW. Antithrombotic therapy in peripheral vascular disease. Chest 1986; 89:75–81.
2. Barnes RW. Noninvasive diagnostic assessment of peripheral vascular disease. Circulation 1991; 83(Suppl 1):1–20.
3. Napel S, Marks MP, Rubin GD, et al. CT angiography with spiral CT and maximum intensity projection. Radiology 1992 Nov; 185(2):607–610.
4. Cambria, RP, Kaufman, JA, L'Italien GJ, et al. Mangnetic resonance angiography in the management of lower extremity arterial occlusive disease: a prospective study. J Vasc Surg 1997; 25:380–389.
5. Quinn SF, Sheley RC, Semonsen KG, et al. Aortic and lower-extremity arterial disease: evaluation with MR angiography versus conventional angiography. Radiology 1998; 206:693–701.
6. Waybill MM, Waybill PN. Contrast media-induced nephrotoxicity: identification of patients at risk and algorithms for prevention. J Vasc Interv Radiol 2001; 12:3–9.
7. Kinney TB, Rose SC. Intraarterial pressure measurements during angiographic evaluation of peripheral vascular disease: techniques, interpretation, applications, and limitations. AJR Am J Roentgenol 1996; 166:277–284.
8. Ligush J, Criado E, Burnham SJ, et al. Management and outcome of chronic atherosclerotic infrarenal aortic occlusion. J Vasc Surg 1996; 24:394–405.
9. Yedlicka JW Jr, Ferral H, Bjarnason H, et al. Chronic iliac artery occlusions: primary recanalization with endovascular stents. J Vasc Interv Radiol 1994; 5(6):843–847.
10. Long AL, Gaux JC, Raynaud AC, et al. Infrarenal aortic stents: initial clinical experience and angiographic follow-up. Cardiovasc Intervent Radiol 1993; 16(4):203–208.
11. Sheeran SR, Hallisey MJ, Ferguson D. Percutaneous transluminal stent placement in the abdominal aorta. J Vasc Interv Radiol 1997; 8(1 Pt 1):55–60.
12. Wescott MA, Bonn J. Comparison of conventional angioplasty with the Palmaz stent in the treatment of abdominal aortic stenoses from the STAR registry. SCVIR Transluminal Angioplasty and Revascularization. J Vasc Interv Radiol 1998; 9(2):225–231.
13. TransAtlantic Inter-Society Consensus (TASC) Working Group. Management of peripheral arterial occlusive disease: TASC document. J Vasc Surg 2000; 31(1 Pt 2):S1–S296.
14. Gardner, GA Jr, Bonn J, Sullivan KL. Quantification of elastic recoil after balloon angioplasty in the iliac arteries. J Vasc Interv Radiol 2001; 12(12):1389–1393.
15. Kandarpa K, Becker GJ, Hunink MG, et al. Transcatheter interventions for the treatment of peripheral atherosclerotic lesions: part I. J Vasc Interv Radiol 2001; 6:683–695.
16. Palmaz JC, Laborde JC, Rivera FJ, et al. Stenting of iliac arteries with the Palmaz stent: experience from a multicentric trial. Cardiovasc Intervent Radiol 1992; 15:291–297.
17. Murphy TP, Webb MS, Lambiase RE, et al. Percutaneous revascularization of complex iliac artery stenoses and occlusions with the use of Wallstent: three-year experience. J Vasc Interv Radiol 1996; 7:21–27.
18. Vorwerk D, Guenther RW, Schurmann K, et al. Primary stent placement for chronic iliac artery occlusions: follow-up results in 103 patients. Radiology 1995; 194(3):745–749.
19. Ballard JL, Taylor FC, Sparks SR, Killeen JD. Stenting without thrombolysis for aortoiliac occlusive disease: experience in 14 high-risk patients. Ann Vasc Surg 1995; 9(5):453–458.
20. Martin EC, Katzen BT, Benenati JF, et al. Multicenter trial of the wallstent in the iliac and femoral arteries. J Vasc Interv Radiol 1995; 6:843–849.
21. Smith GD, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality: The Whitehall Study. Circulation 1990; 82:1925–1931.
22. Sapoval MR, Long AL, Raynaud AC, et al. Femoropopliteal stent placement: long-term results. Radiology 1992; 184(3):833–839.
23. Maynar M, Reyes R, Ferral H, et al. Cragg Endopro System I: early experience. I. Femoral arteries. J Vasc Interv Radiol 1997; 8(2):203–207.
24. Tielbeek AV, Vroegindeweij D, Buth J, Landman GH. Comparison of balloon angioplasty and Simpson atherectomy for lesions in the femoropopliteal artery: angiographic and clinical results of a prospective randomized trial. J Vasc Interv Radiol 1996; 7(6):837–844.
25. Henry M, Amor M, Beyar R, et al. Clinical experience with a new nitinol self-expanding stent in the peripheral arteries. J Endovasc Surg 1996; 3:369–379.
26. Scheinert D, Laird J, Schroder M, et al. Excimer laser-assisted recanalization of long, chronic superficial femoral artery occlusions. J Endovasc Ther 2001; 8:156–166.
27. Duda SH. Presentation of six month follow-up results of the SIROCCO study at the 15th Annual International Symposium on Endovascular Therapy (ISET). SIROlinus Coated Cordis S.M.A.R.T.™ Nitinal Self-expanding Stent for the Treatment of Obstructive superficial femoral artery disease: six-month findings. Miami Beach (FL): 2002 Jan 19–23.
28. Brown KT, Moore ED, Getrajdman GI, Saddekni S. Infrapopliteal angioplasty: long-term follow-up. J Vasc Interv Radiol 1993; 4(1):139–144.
29. Soder HK, Manninen HI, Jaakkola P, et al. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: angiographic and clinical results. J Vasc Interv Radiol 2000; 11(8):1021–1031.

Revascularization of Aortic Arch Branches and Visceral Arteries Using Minimally Invasive Endovascular Techniques

SHYAMKUMAR N. KESHAVA, M.D.[1], AND ABIGAIL FALK, M.D.[2]

Abstract

Minimally invasive techniques as the first line of management in vascular reconstruction are beginning to replace older surgical techniques. General and specific approaches in the endovascular reconstruction of branches off the aortic arch (innominate and subclavian arteries) and the visceral branches off the abdominal aorta (renal and mesenteric arteries) are described. The branches of the aortic arch and the visceral arteries are discussed together because of the similarity in the interventional techniques used for revascularization. Patient selection, endoluminal techniques, complications, and patient management will also be discussed.

Key Words: Endovascular techniques, aortic arch vessels, visceral arteries, renal arteries, mesenteric arteries, minimally invasive techniques.

Introduction

THE DIAGNOSTIC ANGIOGRAPHIC TECHNIQUES explained by Seldinger in 1953 began a new era in the field of vascular disease management (1). In 1964, Dotter and Judkins introduced a new method of treating vascular occlusive disease, a technique that has become known as percutaneous transluminal angioplasty (PTA) (2). Since then, transcatheter endovascular procedures have been used more frequently to treat symptomatic atherosclerosis and other vascular diseases. As we acquire a better understanding of disease processes, and as improvements in medical technology continue, minimally invasive techniques as the first line of management in vascular reconstruction are replacing older surgical techniques. We will describe general and specific approaches in the endovascular reconstruction of branches off the aortic arch (innominate and subclavian arteries) and the visceral branches off the abdominal aorta (renal and mesenteric arteries), discussed together because of similarities in interventional techniques used for revascularization. Patient selection, endoluminal techniques, complications, and patient management will be addressed.

General Principles

Pre-procedural Imaging

An attempt to gain the maximum anatomical information should be made to allow for advanced planning of therapy and thereby to improve patient outcome. These details include status of the aorta, angulation of the artery with the aorta, and status of the visceral organ (i.e. extent of the parenchymal disease in case of renal artery stenosis). Doppler ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and isotope scans are the usual noninvasive modalities to obtain this information. In special circumstances, a diagnostic angiogram may have to be performed as a separate procedure.

Case Selection and Patient Work-up

The relationship of a patient's complaints to vascular compromise must be established by

---

[1] Senior Lecturer, Department of Radiology, Christian Medical College, Vellore, India, and [2] Assistant Professor, Department of Radiology, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Shyamkumar N. Keshava, M.D., Department of Radiology, Christian Medical College, Vellore, India.

history, physical examination and non-invasive studies. Note should be made of hypertension, coagulation status, cardiac and cerebrovascular disease, diabetes, renal insufficiency and patient medications. It is necessary to consult with the concerned medical and surgical specialists caring for the patient so that all management options are considered before the intervention to assure that the patient receives the best possible care. Surgical back up may be required for interventional procedures to manage some rare, but life-threatening potential complications of arterial rupture if necessary. Specifically, before the procedure, the bleeding parameters — prothrombin time (PT), partial thromboplastin time (PTT), platelets — and renal function (creatinine) must be evaluated. In suspected cases of arteritis, intervention should be considered after the erythrocyte sedimentation rate (ESR) becomes normal.

Patient Preparation and Medication

Patients should be fully informed of the procedure, including technical and clinical success rates, long-term outcomes, and any potential complications. An informed consent should be obtained. Understanding the procedure may reduce patient anxiety and yield better cooperation during the procedure. For example, often patients need to hold their breath and not move during digital subtraction imaging. This is best achieved when patients are relaxed and cooperative.

Patients may be admitted to the hospital for same-day surgery. Most often, the procedure can be performed under sedation and local anesthesia. Children and uncooperative/unconscious patients may require general anesthesia. Standard preangiography orders are written, including intravenous hydration and restriction of oral intake to clear fluids after midnight prior to the procedure.

Equipment and Materials

Angiographic equipment capable of digital subtraction is essential. The image intensifier must be large enough to accommodate imaging of the entire abdomen, if necessary. Materials include the following:

- Guiding catheters usually 6F, suitable length and shape according to the orientation and distance from the site of puncture).
- Diagnostic catheters including Pigtail (for aortic flush).
- Simmons, Cobra, Headhunter, Sos-Omni, and Berenstein catheters for selective catheterization.
- Balloon catheters.
- Wires (0.14–0.18" diameter wires, 0.35" diameter wires; exchange length wires 260 – 300 cm).
- Stents ranging from 4 – 10 mm diameter.

Vascular Access

Most commonly, right femoral arterial access is obtained. For renal arterial intervention, ipsilateral femoral approach is preferred. In the visceral branches, which are directed inferiorly, such as the superior mesenteric artery and occasionally the renal and celiac arteries, a brachial approach may be necessary. For a transplant kidney, the approach can be from the contralateral femoral artery.

Contrast Agents

Nonionic iodinated contrast is preferred. If the patient's creatinine is elevated (greater than 1.5 mg/dL), the procedure can be performed with a presumed nephroprotective drug such as fenoldapam (3). Alternative contrast agents include CO_2 and gadolinium (4, 5). The resolution of these alternative contrast agents is less, and depending on the situation, regular contrast may be used for initial and final diagnostic imaging. A dialysis may be planned, if necessary.

Initial Diagnostic Study

Aortic flush angiogram using a 5F pigtail catheter is recommended. The aim is to confirm the extent of the disease by assessing the length of the stenosis, expected diameter and extent of vessel narrowing, orientation of the vessel to the aorta, and condition of the aorta so that a final plan can be developed. The artery should be demonstrated in profile, which may require oblique views (as in renal imaging) or lateral views (as in cases of celiac and superior mesenteric artery imaging). The near accurate length of the diseased segment is best measured in the profiled image of the vessel. Dimension assessment can be made with the help of computer software available in most of the digital subtractions angiography (DSA) machines by comparing the size with a known object like a diagnostic catheter. Intra-arterial pressure gradient measurements across the lesion may help in deciding whether the stenosis is significant or not.

A significant gradient is more than 20 mm Hg. The indications for renal artery intervention are outlined in the Table.

Reaching the Target Site

Access to the target vessel is first achieved with a diagnostic catheter of appropriate configuration. For example, a Headhunter 1 catheter (angular sickle shape) can access the vessels of the aortic arch from the femoral approach, and a reverse curved catheter can access the visceral vessels.

Once access is obtained, the diagnostic catheter may be exchanged for a guiding catheter, which is most often a 6F in size. The guiding catheter should be of appropriate length (enough to be placed in the origin of the artery) and shape so that it stays within the proximal portion of the artery. This allows contrast injection through the guiding catheter to facilitate imaging and proper placement of a balloon or stent once it has crossed the lesion.

A continuous flow of heparinized saline (500 mL normal saline with 2000 units heparin) at a minimal rate should be maintained by connecting the side arm of the vascular sheath to a pressure bag to prevent thrombosis.

TABLE

Indications for Renal Artery Intervention Recommended by Society of Cardiovascular & Interventional Radiology (July 1999)

Renal Artery Angioplasty

Presence of a hemodynamically significant renal artery stenosis (greater than 50% luminal stenosis and/or greater than a 20 mmHg pressure gradient) and there is one of the following conditions:

1. Hypertension that cannot be controlled medically on two drugs of different classifications.
2. There is unexpected deterioration of renal function.
3. There is evidence of loss of renal mass.
4. The etiology is fibromuscular dysplasia.
5. The degree of stenosis is of such a high degree that occlusion is anticipated in the near future.

Renal Artery Stent Deployment

Failure to attain a hemodynamically satisfactory result by renal artery angioplasty as indicated by one of the following conditions:

1. Less than 30% residual renal artery stenosis following balloon angioplasty measured from the outer margins of intimal fissures.
2. Greater than a 20 mm Hg peak systolic residual pressure gradient.
3. Presence of a flow limiting dissection of the renal artery.
4. Restenosis of a lesion that was treated by a technically successful angioplasty in the past.

www.sirweb.org/clinical/pdf/Ind_Renal_Angio.doc

Reconstruction / Revascularization

The stenotic segment may be negotiated with the help of a smaller hydrophilic catheter and a soft tip guide wire to minimize intimal dissection. If the lumen is totally occluded, a 0.18″ diameter wire may be considered. When probing the lesion, a digital vascular roadmap, a feature available on many digital subtraction angiographic units, can be used to direct the manipulations. A roadmap is obtained by contrast medium injection and storage of the resulting image for real-time subtraction during later fluoroscopy. This feature is helpful both for wire placement and balloon/stent placement. Once the catheter is across the lesion, 3,000–5,000 U of heparin is given. An appropriate balloon should be covering the entire length of the stenotic segment, and the diameter should be equal to the expected diameter of the artery. If the stenosis is significant, there may be associated post-stenotic dilatation, which should be kept in mind while deciding the expected diameter. Predilatation may be necessary with a smaller sized angioplasty balloon to facilitate the procedure if the stenosis is severe or a larger balloon catheter cannot be passed across an occlusive segment.

Angioplasty versus Stenting

Most often, stenting has a better initial success rate compared to balloon angioplasty and slightly higher long-term patency (6). A failed balloon angioplasty may require stenting. Stents are avoided in young pediatric patients because stents cannot expand as the patients grow. As a result, the duration of adequate patency may be longer for these patients with surgical intervention than with endovascular treatment.

Assessment of Reconstruction

Anatomical assessment comparing the percentage of patency with that of pre-procedural images can assess immediate success. Physiological assessment of flow and pressure measurements can give a better functional result. In clinical assessment, the patient must demonstrate clinical signs of improvement (i.e., in cases of renal artery intervention, significant reduction in the blood pressure with a corresponding decrease in serum BUN/creatinine levels and antihypertensive medication).

A diagnostic run that demonstrates the vessels distal to the site of reconstruction is essential to exclude complications like embolization.

Complications of Endovascular Revascularization

In general, the complications following endovascular procedures may be related to the puncture site, target site, and contrast material. Specific complications will be briefly described under individual sections.

Post-procedural Care and Follow-up

Unless there is a contraindication, platelet aggregation inhibitors (125 – 325 mg of aspirin orally) should be given prior to the procedure and continued for 3 – 6 months afterward. Additional medication, such as coumadin or clopidogrel bisulfate, may be given, if necessary (7).

Follow-up is usually done by assessing the patient's clinical status and by noninvasive vascular imaging, looking for the recurrence of the initial symptom (mesenteric angina in case of a mesenteric artery stenosis) or a sign (hypertension in case of renal artery stenosis).

Innominate and Subclavian Arteries

Although angioplasty has been performed extensively in the peripheral, renal, and coronary arteries since the 1970s, angioplasty of the supra-aortic arteries began in the 1980s. In the early years, it was done reluctantly, mainly because of the fear of cerebral embolization (8). Innominate and common carotid artery lesions usually have been treated with transthoracic surgery, which has a considerable morbidity and mortality rate (9). However, Hüttl et al. reported on the outcome of 89 patients who underwent innominate artery angioplasties (10). The authors concluded that angioplasty is a safe and effective procedure compared to that of open surgery. There were no deaths, a lower complication rate and an excellent initial success rate. Today, angioplasty/stenting is the treatment of choice in cases of symptomatic innominate artery and subclavian stenosis and short occlusions (10, 11).

The patients usually present with upper limb claudication, transient ischemic attack, or vertebrobasilar insufficiency. The initial diagnosis of innominate artery stenosis or occlusion is based on clinical data, pulse palpation of the radial arteries, comparative blood pressure measurement of both arms, and carotid and vertebral duplex scans. The diagnosis may be confirmed with CTA, MRA, or DSA. Subclavian stenosis with retrograde flow of blood within the vertebral artery may be seen in nearly half of the patients (10). A stenosis of greater than 60% usually requires intervention. Angioplasty is generally carried out via the femoral artery. A long guiding catheter is preferred, keeping the distal end of the catheter near the origin of the target artery. Balloons of a diameter equal to that of the innominate artery just beyond the lesion may be chosen for dilatation (9 – 12 mm) with a length to approximate the diseased arterial segment (usually 2 or 4 cm). In cases of technical difficulties in traversing the lesion with a larger balloon, predilation with a smaller balloon, such as a 3 – 4 mm coronary balloon may be necessary. If the lesion is predilated with a smaller balloon, the larger balloon catheters can then easily cross the diseased segment. There is a general feeling that primary stent deployment is not mandatory; however, it provides a better initial angiographic result and is required when there is a significant residual stenosis following balloon dilation. The primary success rate of innominate angioplasty and stenting has been reported to be greater than 95% (10, 11). Most of the reported interventions involving the innominate arteries were performed with angioplasty alone. However, stent implantation has now become a relatively common part of treating these lesions (12) (Fig. 1). When treating aortic arch vessels, a post procedure angiogram is required not only to confirm a satisfactory radiographic result but also to exclude embolism to the cerebral circulation.

Long-term follow-up includes blood pressure measurements on both arms as well as subclavian, right common carotid, and right vertebral duplex scans. The patency rates of 89% at 5 years (12) for innominate and subclavian artery revascularization is thought to be related to the large vessel size and high blood flow. The complications of innominate and subclavian artery endovascular reconstruction include cerebral infarction (2%), transient ischemic attacks (6%) (10), and mortality 0.2% (12). The use of new protection devices may further decrease the risk of embolization.

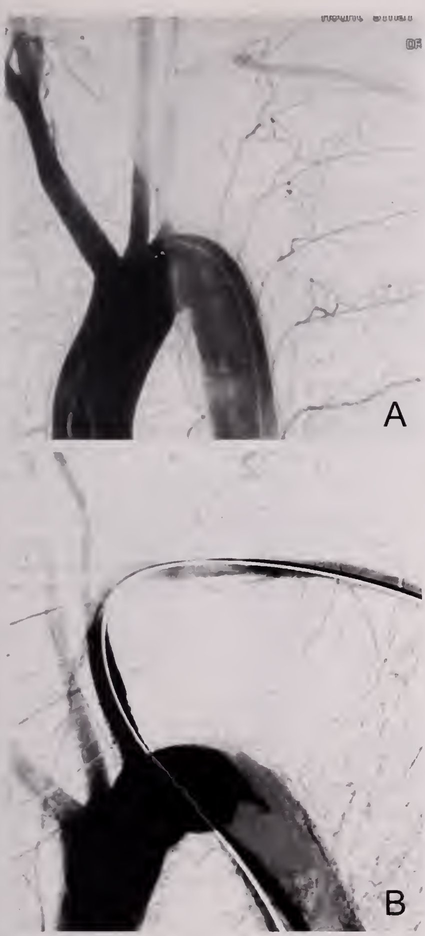

Fig. 1. Fifty-eight-year-old female presenting with left upper extremity claudication. **(A)** Arteriography from a groin approach demonstrates a severe focal stenosis of the left subclavian artery just beyond its origin. **(B)** Following stenting with a balloon expandable stent, full patency of the lumen is restored. The patient's symptoms resolved immediately after the procedure.

Renal Artery

Etiology of renal artery stenosis (RAS) is atherosclerosis in approximately 70% of patients (usually males over 50 years of age). The stenoses are localized mostly in the proximal segment of the renal artery and are ostial in 50% of the patients. In the remaining 30% of the patients, the stenoses are caused by fibromuscular dysplasia (FMD), which, most often, affects younger women.

The main indications for renal artery intervention are renovascular hypertension and ischemic nephropathy. Procedures are considered appropriate for kidneys with long axis exceeding 7–8 cm (Table).

The procedure usually is performed from the ipsilateral femoral approach; the axillary or brachial approaches, less frequent, may be required for the renal arteries with a downward angulation. The size of the most frequently used balloons is 5–8 mm. A guiding catheter with a suitable shape (i.e., hockey stick, cobra) should be selected. Patients with a pressure gradient of greater than 20 mm Hg are good candidates for renal arterial dilatation. The use of pressure gradients often determines whether to intervene or not (13). Balloon mounted stents are preferable compared to the unmounted stents (Figs. 2 and 3).

Stent placement has greatly improved the technical success and long-term patency of atherosclerotic osteal stenosis and main renal artery lesions treated unsuccessfully with angioplasty alone (12). Technical success is nearly 97% with major complications occurring in fewer than 6%. It is essential to demonstrate a good nephrogram with no filling defects at the end of the procedure. Approximately two thirds of patients treated for hypertension with use of stents are cured or have improved blood pressure control at 1-year follow-up. In FMD patients, the clinical success rate is higher, and up to 50% of patients become normotensive (off medication) after successful angioplasty. Stabilization of renal function is seen in nearly three fourths and improvement in 20% of the patients with ischemic nephropathy (12).

Mesenteric Arteries (Celiac/Superior Mesenteric)

Mesenteric angina is an uncommon and difficult diagnosis to make. The incidence has increased significantly over the past few decades because of the increasing number of elderly patients with atherosclerotic disease. Patients with mesenteric angina classically present with colicky abdominal pain following meals (14, 15). Over time, this leads to fear of eating and progressive weight loss. The symptoms, such as nausea, vomiting, diarrhea, and

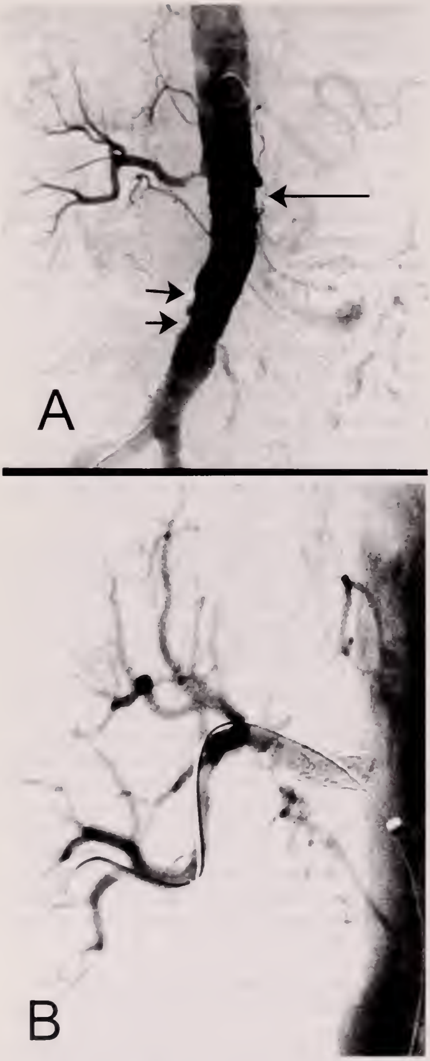

Fig. 2. Seventy-eight-year-old male with uncontrollable hypertension. (A) An aortic flush angiogram shows a severe stenosis in the proximal right renal artery. The left renal artery is completelly occluded (long arrow) and no left nephrogram is identified. Atherosclerotic plaques are seen (short arrows) in the aorta. (B) Images obtained immediately after a balloon expandable stent was placed and dilated to 8 mm demonstrate restoration of the renal artery to its original diameter. Note that predilatation with a 4 mm balloon was necessary to place the mounted stent across the lesion.

occasionally malabsorption, may be more vague (16).

Mesenteric angina occurs when stenosis or occlusion of the mesenteric artery limits blood flow to the intestine. Atherosclerosis is the most common cause and is related to an encroaching plaque located at the ostia of visceral vessels. Other causes are extremely rare. It is believed that 2 of the 3 vessels must be affected for the disease to become symptomatic. The treatment of mesenteric angina aims to restore intestinal blood flow to normal levels. Chronic mesenteric angina requires a high index of suspicion for the diagnosis to be made, and failure to institute treatment can result in high mortality and morbidity.

Usually, a brachial approach is necessary, considering the downward angulation of the vessels. Sometimes, a femoral approach may be necessary, especially if there is an atherosclerotic narrowing of the subclavian artery. A percutaneous transluminal angioplasty (PTA) and stenting are required to treat the stenosis in celiac and superior mesenteric arteries. A coronary stent may be required, considering the small size and sometimes the unusual angle of the vessels to aorta.

PTA and stenting carry a significantly lower morbidity (17) over surgical intervention but may, however, carry the risk of creating arterial spasm, emboli or thrombosis with significant morbidity (17, 18). Nevertheless, the limited evidence in the medical literature indicates that PTA and stenting are relatively safe procedures. The long-term results of this technique still need to be evaluated; the initial results are encouraging (17, 19) (Fig. 4).

Recurrence of the Disease

Recurrence of the stenosis may be due to progression of the disease. Failure to take antiplatelet drugs may result in early stenosis. A recurrent stenosis of an artery can be treated with re-angioplasty and stenting. In-stent restenosis is a therapeutic challenge affecting between 9% and 25% of patients undergoing renal artery stent placement. Despite the reported success of PTA in the treatment of renal artery in-stent restenosis, many patients require further intervention when PTA fails (20). A cutting balloon can be used to achieve technical success when stand-alone PTA fails (21). Repeat stent placement with a resulting "stent sandwich" offers excellent short-term technical success but has the disadvantage of overex-

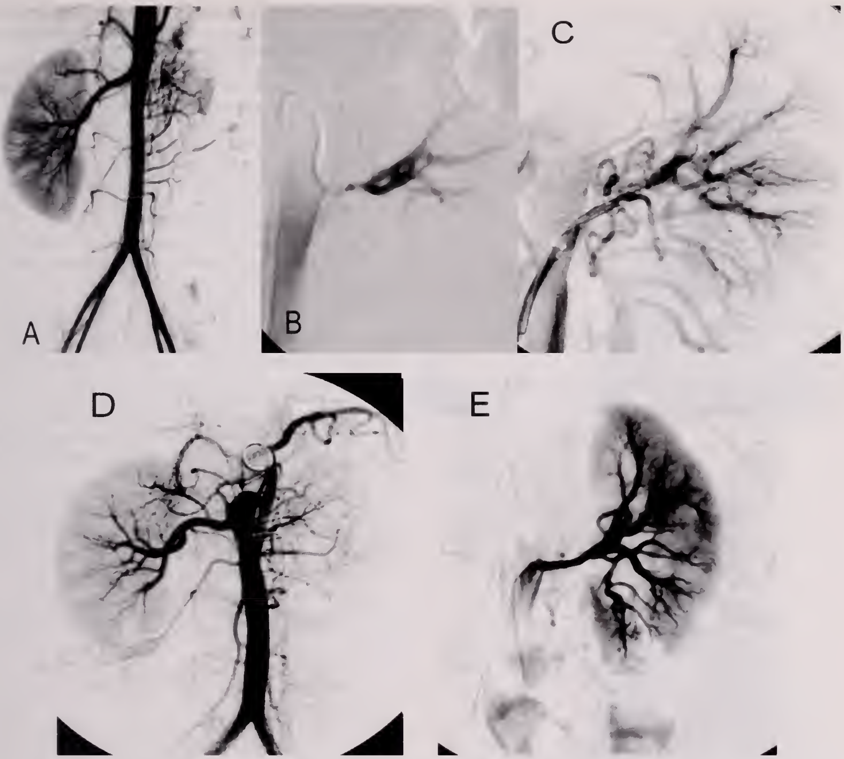

Fig. 3. Twenty-seven-year-old female with uncontrolled hypertension. **(A)** The flush aortogram shows nonopacification of left renal artery. **(B)** Cannulation of the left renal artery with a reverse curved catheter demonstrates near total occlusion of the left renal artery at its origin. **(C)** Predilation with a 3 mm balloon was necessary prior to placement of a stent. A balloon expandable stent was deployed and dilated to 5 mm. The proximal portion of the stent was deliberately placed so that 3 mm projected into the aorta. **(D)** At 6 months, the patient re-presented with the recurrence of uncontrollable hypertension. The patient had discontinued anti-platelet medication after 3 months. The aortogram shows re-occlusion of the left renal artery. **(E)** A selective left renal arteriogram obtained following balloon dilatation with a 5 mm balloon demonstrates full patency of the stent. The patient became normotensive following the repeat intervention.

panding the arterial wall with the potential induction of further neointimal proliferation (22).

Improvements in the stent technology, including drug-coated stents and covered stents, will be useful in the future to reduce restenosis rates. A recent publication examining the ability of endovascular brachytherapy to prevent recurrent in-stent restenosis in patients at high risk for this complication has yielded promising results. Eight (80%) of 10 patients alive at 1 year had no in-stent restenosis apparent on duplex sonography or angiography (23). Animal experiments are being performed to obtain covered stents coated with materials that would reduce the inflammation and intimal hyperplasia (24, 25).

Conclusion

Tremendous advances in the design and fabrication of catheters, wires, balloons, stents, and contrast media have occurred. As a result, "minimally invasive" procedures, which usually do not require an access larger than that to accommodate a 7F catheter, are becoming more common. The initial success rate of most of the revascularization/recon-

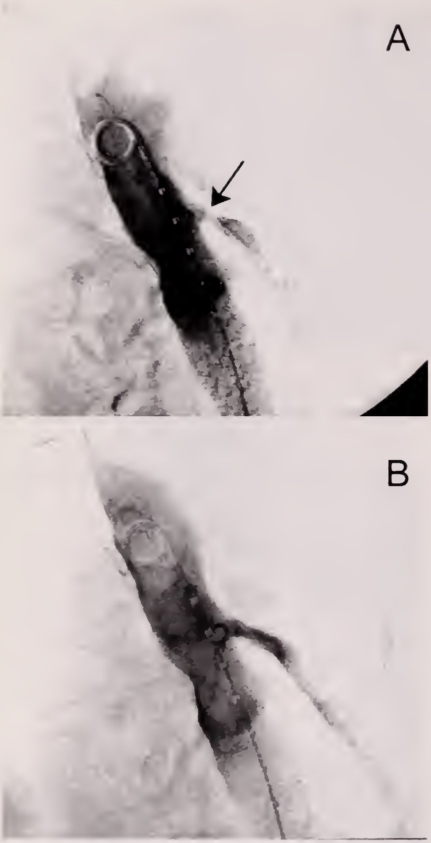

Fig. 4. Sixty-five-year-old female presenting with weight loss over several months and postprandial pain. **(A)** A lateral view of the abdominal aorta demonstrates a focal stenosis (arrow) in the superior mesenteric artery (SMA). **(B)** Following angioplasty with a 5 mm balloon full patency was restored. The patient showed significant clinical improvement.

struction techniques is better than 95% with only limited complications. A remaining problem of restenosis requires a satisfactory solution.

References

1. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography. Acta Radiol 1953; 39:368–376.
2. Dotter C. Judkins MP. Transluminal treatment of arteriosclerotic obstruction description of a new technique and preliminary report of its application. Circulation 1964; 30:654–670.
3. Madyoon H. Croushore L, Weaver D, Mathur V. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. Catheter Cardiovasc Interv 2001; 53(3):341–345.
4. Caridi JG, Hawkins IF, Jr, Klioze SD, Leveen RF. Carbon dioxide digital subtraction angiography: the practical approach. Tech Vasc Interv Radiol 2001; 4(1):57–65.
5. Spinosa DJ, Angle JF, Hartwell GD, et al. Gadolinium-based contrast agents in angiography and interventional radiology. Radiol Clin North Am 2002; 40(4):693–710.
6. Dorros G, Prince C, Mathiak L. Stenting of a renal artery stenosis achieves better relief of the obstructive lesion than balloon angioplasty. Cathet Cardiovasc Diagn 1993; 29(3):191–198.
7. Steinhubl S, Berger P. What is the role for improved long-term antiplatelet therapy after percutaneous coronary intervention? Am Heart J 2003; 145(6):971–978.
8. Hüttl K. Angioplasty of the brachial arteries. In: Zeitler E, editor. Radiology of peripheral vascular disease. New York, Berlin, Heidelberg: Springer; 2000. pp. 607–615.
9. Melliere D, Becquemin J-P, Benyahia NE, et al. Atherosclerotic disease of the innominate artery: current management and results. J Cardiovasc Surg 1992; 33:319–323.
10. Huttl K, Nemes B, Simonffy A, et al. Angioplasty of the innominate artery in 89 patients: experience over 19 years. Cardiovasc Intervent Radiol 2002; 25(2):109–114.
11. Gonzalez A, Gil-Peralta A, Gonzalez-Marcos JR, Mayol A. Angioplasty and stenting for total symptomatic atherosclerotic occlusion of the subclavian or innominate arteries. Cerebrovasc Dis 2002; 13(2):107–113.
12. Kandarpa K, Becker GJ, Hunink MG, et al. Transcatheter interventions for the treatment of peripheral atherosclerotic lesions: Part I. J Vasc Interv Radiol 2001; 12(6):683–695.
13. Gross M, Krämer J, Weingärtner O, et al. Determination of renal arterial stenosis severity: comparison of pressure gradient and vessel diameter. Radiology 2001; 220:751–756.
14. Zelenock GB, Graham LM, Witehouse WM, et al. Splanchnic atherosclerotic disease and intestinal angina. Arch Surg 1980; 115:497–501.
15. Marston A, Clarke JMF, Garcia J, Miller AL. Intestinal functions and intestinal blood supply: a 20-year surgical study. Gut 1985; 26:656–666.
16. Dardik H, Scidenberg B, Parker JG, Hurrvitt ES. Intestinal angina with malabsorption treated by elective revascularization. JAMA 1965; 194:1206–1210.
17. McShane MD, Proctor A, Spencer P, et al. Mesenteric angioplasty for chronic intestinal ischaemia. Eur J Vasc Surg 1992; 6:333–336.
18. Golden DA, Ring EJ, McLean JK, Freiman DB. Percutaneous transluminal angioplasty in the treatment of abdominal angina. AJR Am J Roentgenol 1982; 139(2):247–249.
19. Mohammed A, Teo NB, Pickford IR, Moss JG. Percutaneous transluminal angioplasty and stenting of coeliac artery stenosis in the treatment of mesenteric angina: a case report and review of therapeutic options J R Coll Surg Edinb 2000; 45(6):403–407.
20. Bakker J, Goffette PP, Henry M, et al. The Erasme study: a multicenter study on the safety and technical results of the Palmaz stent used for the treatment of atherosclerotic ostial renal artery stenosis. Cardiovasc Intervent Radiol 1999; 22:468–474.
21. Munneke GJ, Engelke C, Morgan RA, Belli AM. Cutting balloon angioplasty for resistant renal artery in-stent restenosis. J Vasc Inter Radiol 2002; 13:327–331.
22. Di Mario C, Marsico F, Adamian M, et al. New recipes for in-stent restenosis: cut, grate, roast, or sandwich the neointima? Heart 2000; 84:471–475.
23. Stoeteknuel-Friedli S, Do DD, Von Briel C, et al. Endovascular brachytherapy for prevention of recurrent renal in-stent restenosis. J Endovasc Ther 2002; 9(3):350–353.

24. Sangiorgi G, Arbustini E, Lanzarini P, et al. Nonbiodegradable expanded polytetrafluoroethylene-covered stent implantation in porcine peripheral arteries: histologic evaluation of vascular wall response compared with uncoated stents. Cardiovasc Intervent Radiol 2001; 24(4):260–270.

25. Klugherz BD, Llanos G, Lieuallen W, et al. Twenty-eight-day efficacy and phamacokinetics [sic] of the sirolimus-eluting stent. Coron Artery Dis 2002; 13(3):183–188.

Endovascular Repair of Diffuse Atherosclerotic Occlusive Disease Using Stented Grafts

EDWIN C. GRAVEREAUX, M.D.[1], AND MICHAEL L. MARIN, M.D.[2]

Abstract

Minimally invasive techniques have greatly influenced the practice of surgery in the past two decades, especially the vascular surgical specialty. Current technological advances and refinements have allowed for the application of less invasive or percutaneous endovascular techniques to the treatment of arterial aneurysms and peripheral vascular occlusive disease. While balloon angioplasty and stenting for occlusive disease have proven successful in certain vascular beds (such as common iliac arteries), infrainguinal results are generally less impressive.

This paper reviews the results of the application of covered stent-grafts to peripheral arterial occlusive disease, both at the aortoiliac and infrainguinal anatomical levels. The review includes the results of iliac artery stented graft placement utilizing a combined open surgical and endovascular technique at Mount Sinai Medical Center.

Key Words: Endovascular, stent-graft, iliac artery, superficial femoral artery, minimally invasive, peripheral vascular disease.

Introduction

THE APPLICATION of endovascular techniques to the treatment of arterial occlusive disease has become a focus of much interest among physicians treating patients with peripheral vascular disease. Initially, endovascular therapy was seen as an attractive alternative to traditional open surgical management for patients with multiple medical comorbidities placing them in high or prohibitive surgical risk categories. More recently, with the improvement of biomedical devices and techniques, many more specialists who treat vascular diseases have proposed the use of minimally invasive treatment.

Completely percutaneous, as well as combined endovascular approaches coupled with limited open surgical exposures, have been described for recanalization of arterial occlusive disease. Although the accumulated experience and reports of endovascular stented-graft treatment of arterial occlusive disease are relatively limited, the allure of less-invasive treatment has led to new strategies and device designs. Currently available devices and applied techniques are highlighted in this paper, especially the use of endografts in atherosclerotic arterial occlusive disease of the iliac arteries and lower extremities.

Development and General Techniques

Reports by Dotter (1) in 1983, on a transluminally expanded nitinol-coiled (nickel-titanium polymer) stented graft, and Volodos (2) in 1986, on a Dacron-covered Z-stent for recanalization of an iliac artery occlusion, provided the first descriptions of endovascular stent-grafting for treatment of arterial occlusive disease. Early percutaneous treatment for superficial femoral artery (SFA) and popliteal artery occlusive disease, utilizing the Cragg Endopro Stentgraft (Mintec Corp, Grand Bahamas) was subsequently described. It was theorized that stented grafts might decrease recurrence of some of the early lesions following SFA balloon angioplasty, with or without adjuvant stenting (3, 4). At present, several devices have been developed and applied to endoluminal treatment of

---

[1] Instructor of Surgery and Interventional Cardiovascular Medicine, Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA and [2] Chief and Professor of Surgery, Division of Vascular Surgery, Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Edwin C. Gravereaux, M.D., Brigham and Women's Hospital, Division of Vascular Surgery, 75 Francis Street, Boston, MA 02115.

arterial occlusive disease. They range from homemade devices, utilizing hand-sewn Palmaz (Cordis, Miami, FL) stents to polytetrafluoroethylene (PTFE) grafts, to industry-made stent-grafts, including the Passager (Boston Scientific, Natick, MA) (formerly, the Cragg Endopro), the Jostent (Jomed, Atlanta, GA), and the Viabahn (latest update of the Hemobahn, WL Gore, Flagstaff, AZ) (Fig 1).

General technical considerations for use of these devices include the need to first recanalize the severely stenosed or occluded arterial segment, often by use of a hydrophilic guidewire, and ensuring re-entry into the true lumen either proximal or distal to the lesion. Balloon dilation is then often used to re-establish luminal diameter, after which the stented graft is deployed and secured proximally and distally by stents, if not already fully supported throughout its length. Subsequent post-deployment balloon angioplasty can be employed to achieve full graft expansion and wall apposition.

Aortoiliac Level Disease

In the iliac artery, recanalization of occlusions can be performed percutaneously by both the ipsilateral (retrograde) and contralateral ("up-and-over" or anterograde) approaches. Percutaneous transluminal angioplasty (PTA) and stenting have been shown to have both high technical success rates and durability approaching that of the traditionally preferred open-surgical aorto-bi-femoral bypass grafting, with 5-year patency rates greater than 90% (5). Shortcomings include higher rates of restenosis and failure in total occlusions and long-segment disease, and limitations in the simultaneous management of femoral and outflow disease. Indications for endoluminal stented graft use in iliac disease range from claudication to acute limb ischemia. Use of a stent-graft for prevention of embolization by covering a large iliac thrombus has also been reported (6).

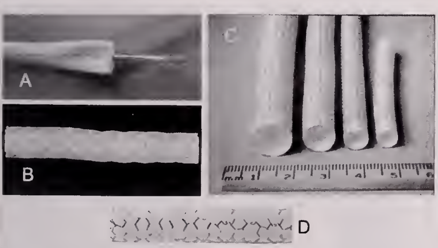

Fig. 1. (A) Homemade endovascular stent-graft: Palmaz stent sutured to polytetrafluoroethylene (PTFE) graft. **(B)** Cragg Endopro: a nitinol self-expanding stent is covered by a polyester fabric material. **(C)** Viabahn: an exoskeleton of self-expanding nitinol coils supports an expanded PTFE lining. **(D)** Jostent: an ultrathin layer of ePTFE between two stainless steel stents.

The technique utilized at Mount Sinai Medical Center for management of long-segment iliac artery occlusion is based on the potential benefit of using covered stents in combination with surgical femoral artery exposure and arteriotomy. With this combined surgical and endovascular strategy, external iliac and femoral artery disease can be addressed, thus expanding the application of endoluminal techniques to those patients who would not be candidates for a purely percutaneous approach. The procedures are performed in the operating room, preferably under spinal/epidural anesthesia. Following femoral artery cutdown, angiographic sheaths are placed to allow guidewire and directional catheter recanalization of the occluded iliac artery from either an anterograde or retrograde approach (Fig. 2A, B). Balloon dilation of the artery is then performed with an 8 mm angioplasty balloon (Fig. 2C). With vessel-loop control of the artery, the sheath is removed, an arteriotomy is made, and insertion of the fabricated delivery system is performed under fluoroscopic guidance over the guidewire (Fig. 2D). The stent graft is fashioned by suturing a Palmaz stent to a PTFE graft, crimping the stent over a balloon catheter, and furling the assembled graft within a long sheath equipped with hemostatic valves and a leading balloon forming a proximal tapering (Fig. 3). When the device is properly positioned in the proximal iliac artery, the sheath is withdrawn, the leading balloon is deflated and withdrawn, and the Palmaz stent and attached stent-graft are deployed. The distal end of the PTFE graft is brought down through the arteriotomy, and further balloon inflation of the length of the graft is carried out along with angiography via an attached large French angiographic sheath. The distal graft anastomosis is then created surgically according to the pattern of outflow disease (Fig. 4). The following example case report serves to illustrate the technique.

Illustrative Case

A 76-year-old woman with severe coronary artery disease, untreated critical 90% left carotid stenosis, emphysema, and known pe-

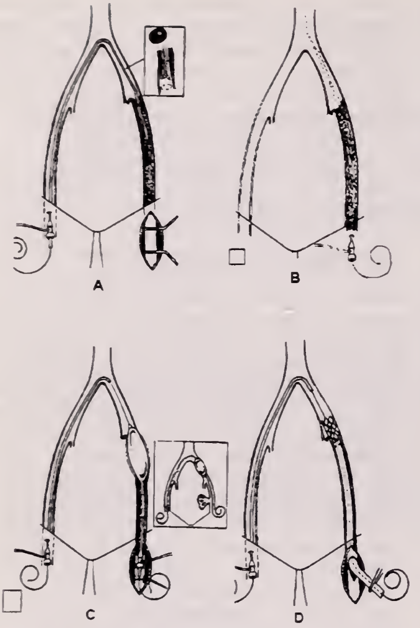

Fig. 2. (**A**) Anterograde directional catheter and wire recanalization of iliac occlusion. (**B**) Retrograde recanalization. (**C**) Balloon dilation of recanalized iliac segment. (**D**) Deployed homemade stent-graft. A Palmaz stent sutured to the PTFE graft secures the proximal graft. The distal graft is brought out through the arteriotomy.

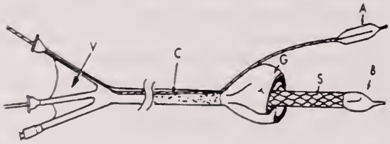

Fig. 3. Delivery system fashioned for aortoiliac endograft insertion and deployment. The lead balloon (A) forms a tapered tip for the delivery sheath (C). The stent-graft is contained within the delivery sheath, with the graft (G) sutured to the Palmaz stent (S). With inflation of the lead balloon (A) and closure of the hemostatic valves (V), fluid pressurization of the sheath provides rigidity to facilitate insertion up the iliac artery over a guidewire. With the outer sheath retracted, inflation of the second balloon (B) deploys the Palmaz stent and the graft.

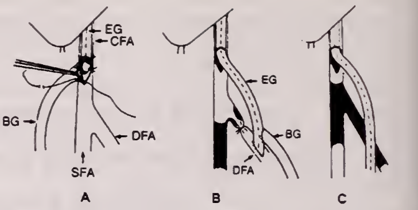

Fig. 4. Options (**A, B, C**) for creating distal anastomoses at the femoral arteriotomy with distal limb bypass extension. EG = endograft; CFA = common femoral artery; DFA = deep (profunda) femoral artery; SFA = superficial femoral artery; BG = bypass graft.

ripheral vascular disease (prior left and right iliac PTA and stenting) underwent an outpatient angiogram via a right femoral approach during work-up for chronic mesenteric ischemic symptoms. Recurrent stenosis of her right external iliac artery (EIA) stents was noted. Twelve hours after the angiogram, she presented to the emergency room with acute right leg ischemia, manifested by a cold, pulseless foot with mild sensory deficit. Urgent repeat angiogram revealed occluded right EIA and common femoral artery (CFA) with reconstituted profunda femoral artery and occluded superficial femoral artery (SFA) (Fig. 5). She was immediately brought to the operating room and was given spinal anesthesia; right SFA exposure was performed, a 5F sheath was placed, and a hydrophilic guidewire was maneuvered across the occlusion. Systemic heparin was administered and balloon angioplasty of the right iliac system was performed with an 8 mm balloon (Fig. 6). The stent-graft device was created on a sterile back-table and inserted over the guidewire after femoral arteriotomy was created. Under fluoroscopic guidance, the insertion sheath device

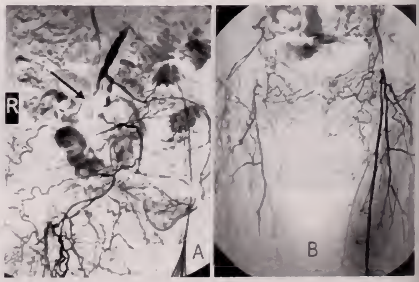

Fig. 5 (**A**) Preoperative selective right iliac angiogram showing external iliac artery occlusion within remotely placed stent (arrow). (**B**) Iliofemoral angiogram showing occluded right external iliac, common femoral, and superficial femoral arteries.

was positioned, the outer sheath withdrawn, and the stent-graft deployed (Fig. 7). The distal end of the PTFE graft is shown emerging from the common femoral arteriotomy. A shortened angiographic sheath was attached to the distal end of the PTFE graft for postdeployment balloon dilation of the graft (Fig. 8). Completion retrograde angiogram showed a widely patent result (Fig. 9). The distal graft end was then anastomosed to the right profunda femoral artery (PFA) (Fig. 10). The patient had restoration of pedal Doppler signals with alleviation of her symptoms. She was discharged on postoperative day two.

Utilization of the above technique was initially reported by Marin in 1995 (7). Wain et al. (8) reported further data on 52 high-morbidity patients who underwent this technique for critical limb ischemia, with half requiring concomitant adjunctive infrainguinal bypass. These patients were prohibitive surgical risks for open aortoiliac bypass. Initial procedural success was 93%. The respective 5-year primary and secondary patency rates were 66% and 77%, with a limb-salvage rate of 88%.

Infrainguinal Arterial Level

For arterial occlusive disease of the femoropopliteal region, consistently inferior patency has been seen for endoluminal stent-grafting when compared to both endovascular techniques applied to iliac occlusive disease and to open infrainguinal bypass surgery. However, the allure of minimally invasive treatment for the femoral artery has resulted in the trial of several devices and techniques.

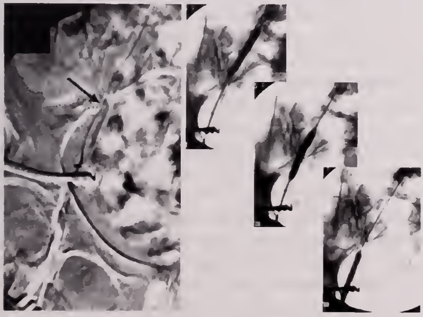

Fig. 6. Left panel: Retrograde hydrophilic guidewire recanalization (arrow) of iliac occlusion. **Right panel:** Sequential balloon dilation of iliac artery.

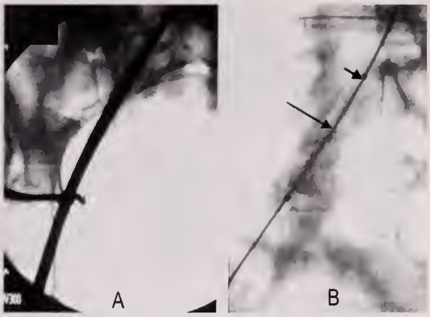

Fig. 7 (A) Insertion of deployment sheath containing stent-graft. **(B)** Outer sheath withdrawn and proximal stent-graft is positioned. Long arrow denotes proximal edge of undeployed Palmaz stent premounted on deployment balloon; short arrow identifies balloon proximal marker.

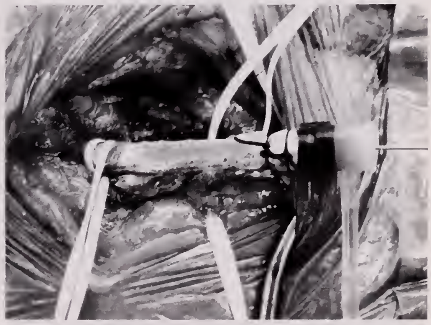

Fig. 8. Distal PTFE graft emerging from SFA, with shortened angiographic sheath attached to allow postdeployment balloon angioplasty and angiography.

Generally poor outcomes for percutaneous transluminal angioplasty (PTA), with or without stenting, of long-segment SFA stenosis or occlusion have led to attempts to reline the SFA with an endoluminal bypass following recanalization. The endoluminal graft can be fully supported by stents along its length, or it can utilize a PTFE graft anchored by stents at one or both ends. Theoretical benefits for this approach include a potentially less invasive procedure, an in-line "end-to-end" reconstruction with resultant hemodynamic improvements compared to an end-to-side surgical bypass, and the possibility of future surgical revascularization, should the procedure fail. A potential neg-

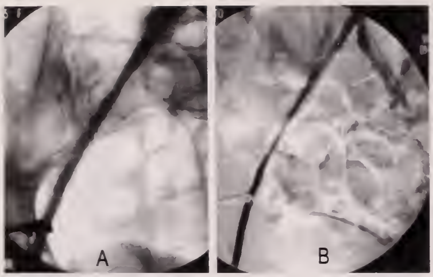

Fig. 9. Completion angiography (retrograde) of stent-grafted right iliac artery. **(A)** shows a magnified view of the stent-graft repair of the right iliac system. **(B)** shows the wider view of the retrograde contrast injection opacifying the aortic bifurcation and proximal left iliac artery (arrow).

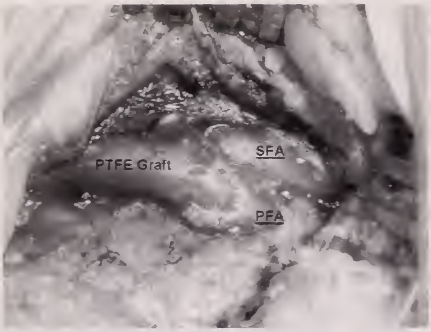

Fig. 10. PTFE graft surgical anastomosis to profunda femoral artery (PFA). Superficial femoral artery (SFA) is occluded.

ative effect, however, is the covering of any collateral side branches, something avoided by use of uncovered stents.

Disputed issues include whether or not the SFA requires debulking of the lesion prior to endoluminal graft deployment. Several techniques have utilized percutaneous recanalization with PTA without debulking the lesion. Results of nondebulking trials have been variable, and most reports have been of immediate and short-term follow-up, with little long-term data. The initial report of the use of the Cragg Endopro (now the Passager) graft demonstrated immediate procedural success in the eight treated patients, with primary patency in six of these cases during early follow-up (3). Later follow-up, however, showed all grafts to be occluded at 2 years (9). Henry's data on the Passager graft demonstrate 94% procedural success, with 75% secondary patency at 8-month follow-up (4). Another report utilizing this stent-graft had 45% and 56% primary and secondary patency rates, respectively, for ten patients at 17 months (10).

Diethrich utilized a PTFE/Palmaz stent combination delivered via percutaneous access in 50 patients; he reported primary patency of 65% and secondary patency of 85% at 8 months, with six acute postoperative occlusions (11). Longer follow-up exhibited primary patency of 46% and secondary patency of 68% at 2 years (12). Salvage procedures included use of thrombolysis and surgical thrombectomy. Seven patients required surgical femoral-popliteal bypass after occlusion of their endografts.

Other authors have advocated intra-operative endograft deployment via surgical femoral artery exposure and arteriotomy. After balloon angioplasty of the SFA, Marin created a sutured proximal anastomosis of the proximal end of an unsupported PTFE graft to the native femoral artery, and then fixed the distal graft end to the distal vessel with a Palmaz stent. At 18 months, only one graft remained patent in the seven patients on whom the procedure was performed (13). Spoelstra reported one-year follow-up for 55 patients, utilizing the same technique described above, with overdilation of the SFA with a 9 mm angioplasty balloon. Early primary patency was 73% and secondary patency 86%. Long-term follow-up was not reported (14).

With early experience using the percutaneously deployed Hemobahn device in the SFA after PTA, Bleyn showed 6-month primary patency of 83%, with 86% secondary patency (15). Two-year follow-up data on the Hemobahn device, as reported by Dake, revealed 65% and 90% primary and secondary patency, respectively (16). More recent reports have revealed a high rate of technical success in deployment and early angiographic result, but mixed results regarding patency. Bauermeister recanalized long-segment occlusions in 35 patients and successfully deployed Hemobahn stent-grafts. Adjuvant thrombectomy techniques were employed in the majority (ring cutter, balloon thrombectomy, thrombolsysis), and 16 required adjuvant surgical procedures (femoral bifurcation patch angioplasty). One-year primary and secondary patency were 73% and 82%, respectively, by life-table analysis (17). Deutschmann and colleagues successfully placed Hemobahn stent-grafts in 17 of 18 patients. Primary patency at 3 months was 61%, dropping to 49% at 6-month follow-up. Secondary patency improved 6-month patency results to 61%. Patency was seen to be decreased for stented segments longer than 10 cm and intimal hyperplasia was observed in 39%, at either the proximal or distal ends of the stent-graft (18). Ahmadi reported a 17% rate of early occlusion (within 24 hours) in a series of 30 patients who underwent PTA of SFA with placement of a Dacron-covered stent-graft. Restenosis was observed in 83% of patients at mean follow-up of 5 years, with primary patency rates of 23%, 17%, and 17%, respectively, at 1, 3, and 5 years. Secondary patency rates were 60%, 34%, and 34%, respectively. Patients were maintained on warfarin and aspirin (19).

As previously mentioned, the second technique of stent-grafting for SFA disease employs surgical debulking of plaque prior to relining the lumen with a PTFE graft. Bergeron and Ho described SFA endarterectomy with the Mollring Cutter (Fig. 7), followed by endovascular placement of the PTFE graft (20, 21). Ho and associates' technique evolved from initial Mollring SFA endarterectomy alone with stenting for fixation of the distal endarterectomy flap, to relining the endarterectomized SFA with PTFE. Of Bergeron's 17 patients treated with semi-closed Mollring endarterectomy and PTFE relining, three experienced early re-occlusion, requiring surgical bypass, and two others needed interventional adjunctive stent placement to maintain patency (22). Ho's results exhibited one-year primary and secondary patency rates of 76% and 78%, with two-year primary and secondary patency rates of 61% and 70% (23). At the 2000 VEITH symposium, Moll presented data on 40 patients treated as described above, with 6-month follow-up having an 81% secondary patency rate (24).

Morris (25) has employed wire-guided rotational and nonrotational remote endarterectomy devices (EVI, Vancouver, Canada) to clear the SFA of plaque, sequentially upsizing the size of the endarterectomy catheter, followed by PTA. He then uses endoluminal forceps to pass the PTFE graft through the newly cleared lumen. He creates a surgically sutured proximal anastomosis at the arteriotomy site, while the distal end of the PTFE graft is left unanchored (without stent fixation), hoping to decrease neointimal hyperplasia at this site. Morris reports that 12 of 14 patients had successful treatment with the EVI endarterectomy and PTFE relining. Three had immediate failures (all cleared with thrombolysis), two additional failures at 2 months, and two-year primary and secondary patencies of 61% and 70%, respectively (25). Bergeron also reported on the use of the EVI device, with his eight patients having 100% patency six months after the procedure (26).

Summary

The past decade has witnessed an acceleration in the interest in minimally invasive treatment of peripheral vascular disease. As described in the above overview, the application of endovascular techniques using stented grafts has brought success in the treatment of arterial occlusive disease, particularly in the aortoiliac arterial bed. For the femoropopliteal arterial location, novel strategies involving both percutaneous and combined open and catheter-based techniques have shown promising results in the short-to-intermediate term, particularly for those patients at high risk for conventional surgery. Careful patient selection and diligent long-term follow-up is mandatory. Continuing application of technical advances and a targeting of the causes of failure, such as graft stenosis, kinking, and intimal hyperplasia, await long-term outcome studies.

References

1. Dotter CT, Buschmann RW, McKinney MK. Transluminal expandable nitinol coil stent grafting: preliminary report. Radiology 1983; 147:259–260.
2. Volodos NL, Shekhanin VE, Karpovich IP, et al. Self-fixing synthetic prosthesis for endoprosthetics of the vessels [in Russian]. Vestn Khir Im I I Grek 1986; 137:123–125.
3. Cragg AH, Dake MD. Percutaneous femoropopliteal graft placement. J Vasc Interv Radiol 1993; 4(4):455–463.
4. Henry M, Amor M, Ethevenot G, et al. Initial experience with the Cragg Endopro System I for intraluminal treatment of peripheral vascular vessels. J Endovasc Surg 1994;1:31–43.
5. Onal B, Ilgit ET, Yucel C, et al. Primary stenting for complex atherosclerotic plaques in aortic and iliac stenoses. Cardiovasc Intervent Radiology 1998; 21:386–392.
6. Liistro F, Stankovic G, Di Mario C, et al. Covered stent to exclude intravascular thrombus. J Endovasc Ther 2002; 9(2):246–249.
7. Marin ML, Veith FJ, Sanchez LA, et al. Endovascular aortoiliac grafts in combination with standard infrainguinal arterial bypasses in the management of limb-threatening ischemia: preliminary report. J Vasc Surg 1995; 22:316–325.
8. Wain RA, Veith FJ, Marin ML. Analysis of endovascular graft treatment for aortoiliac occlusive disease: what is its role based on mid-term results? Ann Surg 1999; 230:145–151.
9. Cragg AH, Dake MD. Treatment of peripheral vascular disease with stentgrafts. Radiology 1997; 205:307–314.
10. Maynar M, Reyes R, Ferral H, et al. Cragg Endopro System I: early experience. I. Femoral arteries. J Vasc Interv Radiol 1997; 8:203–207.

11. Diethrich EB, Papazoglou K. Endoluminal grafting for aneurysmal and occlusive disease in the superficial femoral artery: early experience. J Endovasc Surg 1995; 2:225–239.
12. Rodriguez-Lopez JA, Soler L, Werner A, et al. Long-term follow-up of endoluminal grafting for aneurysmal and occlusive disease in the superficial femoral artery. J Endovasc Surg 1999; 6:270–277.
13. Marin ML, Veith FJ. Endovascular stented grafts in the treatment of aortoiliac and femoropopliteal occlusive disease. Presented at the 21st annual symposium, Current Critical Problems in Vascular Surgery; Nov. 21–23, 1994; New York.
14. Spoelstra H, Casselman F, Lescu O. Balloon-expandable endobypass for femoropopliteal atherosclerotic occlusive disease: a preliminary report of fifty-five patients. J Vasc Surg 1996; 24:647–654.
15. Bleyn JFS, Vanhandenhove I. Femoropopliteal endobypass using the Hemobahn for occlusive disease: results and lessons learned [abstract]. J Endovasc Surg 1999; 6:80.
16. Dake M, Semba C, Kee S, et al. Results of a multicenter feasibility study of the Hemobahn stent-graft in iliofemoral occlusive disease [abstract]. J Endovasc Surg 1999; 6:188.
17. Bauermeister G. Endovascular stent-grafting in the treatment of superficial femoral artery occlusive disease. J Endovasc Ther 2001; 8(3):315–320.
18. Deutschmann HA, Schedlbauer P, Berczi V, et al. Placement of Hemobahn stent-grafts in femoropopliteal arteries: early experience and mid-term results in 18 patients. J Vasc Interv Radiol 2001; 12(8):943–950.
19. Ahmadi R, Schillinger M, Maca T, et al. Femoropopliteal arteries: immediate and long-term results with a Dacron-covered stent-graft. Radiology 2002; 223(2):345–350.
20. Bergeron P. Stenting and endoluminal grafting of femoral and popliteal arteries. J Endovasc Surg 1995; 2:197–198.
21. Ho GH, Mool FL, Joosten PP, et al. The Mollring Cutter remote endarterectomy: preliminary experience with a new endovascular technique for treatment of occlusive superficial femoral artery disease. J Endovasc Surg 1995; 2:278–287.
22. Bergeron P, Chiarandini S, Naza G, et al. Femoral artery endoluminal bypass grafting: indications and early results. J Endovasc Surg 1997; 4:404–405.
23. Ho GH, Moll FL, Tutein Nolthenius RP, et al. Endovascular femoropopliteal bypass combined with remote endarterectomy in SFA occlusive disease: initial experience. Eur J Vasc Endovasc Surg 2000; 19:27–34.
24. Moll FL. Remote endarterectomy with or without an endograft lining for long SFA occlusions. Presented at the 27th annual VEITH Meeting; Nov. 20–24, 2000; New York.
25. Morris GE, Tisi PV. Endovascular femoropopliteal bypass. In: Moore WS, Ahn SS, editors. Endovascular Surgery. Philadelphia (PA): WB Saunders, Co.; 2001.
26. Bergeron P, Chambran P, Manes L, et al. SFA endovascular bypass combined with endarterectomy. J Endovasc Surg 1999; 6:184–185.

Drug-Eluting Stents in Peripheral Vascular Disease:

Eliminating Restenosis

Sharif H. Ellozy, M.D., and Alfio Carroccio, M.D.

Abstract

Transcatheter endovascular therapy for peripheral atherosclerotic disease has become more popular. In general, good results have been reported in focal aortoiliac disease. However, the long-term patency of angioplasty in longer, more distal lesions has been less satisfactory. Stenting has not been shown to improve long-term patency compared to angioplasty alone. Drug-eluting stents have shown promise in preventing coronary restenosis, and preliminary results in peripheral arterial disease are encouraging. This review article will discuss the current status of endovascular therapy of aortoiliac and femoropopliteal atherosclerotic disease, the theoretic and experimental basis for the use of drug-eluting stents, and the preliminary results in human studies.

Key Words: Drug-eluting stents, peripheral artery occlusive disease, restenosis.

Introduction

Restenosis is the Achilles heel of endovascular therapy for occlusive disease. Immediate technical success of percutaneous angioplasty and stenting for aortoiliac and superficial femoral artery disease is upwards of 90% (1, 2). However, acute occlusion in the periprocedural period and late restenosis have limited long-term patency. While stent placement may decrease the risk of long-term failure in aortoiliac disease, it has not improved long-term patency rates over balloon angioplasty alone in superficial femoral artery disease, possibly due to an increase in neointimal hyperplasia (1 – 3). Therapy aimed at preventing restenosis may be the key to achieving good long-term results with endovascular techniques.

The response of the artery to balloon dilatation can be divided into four phases, each of which contributes to restenosis:

- the mechanical phase, which may be complicated by early elastic recoil;
- the thrombogenic phase, which is characterized by mural thrombus formation secondary to local hemorrhage and thrombosis;
- the proliferative phase, which is typified by neointimal hyperplasia;
- the remodelling phase, with pathologic changes in the cellular and protein content of the media and adventitia (4).

Stenting has largely eliminated elastic recoil as a cause of restenosis. Therapeutic anticoagulation and antiplatelet therapy are used to prevent thrombosis. Currently, numerous antiproliferative agents, including sirolimus, are under investigation for the prevention of neointimal hyperplasia as a cause of late restenosis.

Sirolimus is a hydrophobic product of the actinomycete *Streptomyces hygroscopicus*. It was initially discovered as an antifungal agent, but was never used because of its immunosuppressive effects. The FDA finally approved it for use as an immunosuppressant in 1999. As a hydrophobic drug, it passes directly through the cell membrane to bind to cytosolic FK506 binding proteins (FKBP). This binding then increases the levels of p27, a ubiquitous cyclin-

---

Assistant Professor of Surgery, Division of Vascular Surgery, Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Sharif H. Ellozy, M.D., Department of Surgery, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; e-mail: sharif.ellozy@msnyuhealth.org

dependant kinase inhibitor, which ultimately interrupts progression of the cell cycle from G1 to S phase (Fig. 1). Medial vascular smooth muscle cells are quiescent (G0). In response to injury, they enter the G1 phase. Sirolimus has been shown to inhibit cell-cycle progression in a variety of cells, including fibroblasts, endothelial cells, smooth muscle cells. Animal studies have shown the maximum rate of proliferation to occur within three to seven days of angioplasty (4). Sustained release of sirolimus from coated stents was confirmed for up to 28 days in a rabbit iliac model, with levels in the blood being undetectable at 2 days. The reduction in neointimal hyperplasia was dose dependent (5). Pharmacokinetic modelling of stent based drug delivery systems suggests that hydrophobic drugs achieve higher mean tissue concentrations and remain closer to the intima. (6). They are also less prone to diffusive backwash into the circulation. This may explain why hydrophobic drugs such as sirolimus and paclitaxel have shown more success in limiting restenosis than hydrophilic drugs such as heparin.

Early results with sirolimus coated stents in human coronary arteries have been impressive. The RAVEL study, a randomized clinical trial comparing a sirolimus coated stent with a standard (uncoated) stent, showed restenosis of 50% or more in none of those receiving treatment but in 26.6% of those in the control group ($p<0.001$) (7). The difference in stenosis correlated with a significant increase in the rate of major cardiac events in the uncoated group.

Such promising results in the coronary circulation led to the investigation of drug-eluting stents in peripheral occlusive disease (Figs. 2, 3). The SIROCCO(Sirolimus Coated Cordis SMART Nitinol [nickel-titanium polymer] Self-expandable stent for the treatment of Obstructive Superficial Femoral Artery Disease) study is a multicenter, feasibility study looking at the use of drug-eluting stents in superficial femoral artery disease (8). Thirty-six patients were enrolled in a double-blinded, randomized, prospective fashion. Sirolimus and a co-polymer were bonded in a thin, uniform layer (5 – 10 &M) to a Cordis SMART nitinol self-expanding stent. The final drug dose was 1.2 mg/stent, and the stents were 6 – 7 mm in diameter and 8 cm long. Inclusion criteria were symptomatic ischemia, unilateral superficial femoral artery (SFA) stenosis or occlusion, stenotic lesion length between 7 and 20 cm or occlusion be-

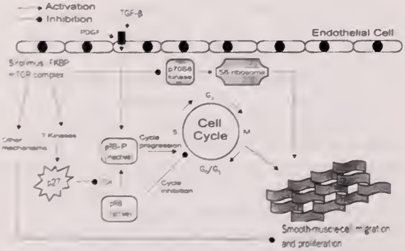

Fig. 1. Artist's drawing of the cell cycle inhibitory events associated with sirolimus therapy for the suppression of neointimal hyperplasia.

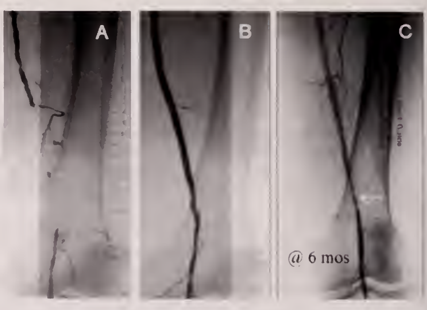

Fig. 2. Superficial femoral artery occlusive disease. (**A**). A 12 cm long total occlusion of the superficial femoral artery is seen on this contrast angiogram. (**B**). Following recanalization and balloon angioplasty and stenting, circulation is re-established to the lower extremity. (**C**). Six months following stent implantation, in-stent restenosis is seen (arrow).

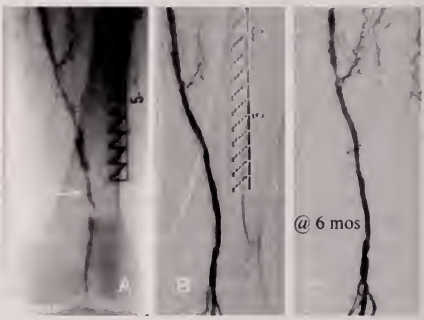

Fig. 3. Superficial femoral artery occlusive disease. (**A**). Contrast angiogram of a long segment showing stenosis (arrow). (**B**). Following balloon angioplasty and implantation of a sirolimus coated stent, arterial continuity is restored. (**C**). Six month follow-up angiogram of same patient as shown in panel B. No in-stent restenosis is seen.

tween 4 and 20 cm, a limit of three stents to correct the lesion, and a patent popliteal artery. Exclusion criteria were tandem lesions, poor inflow, scheduled revascularization of the same limb within 30 days of stenting, a previous stent at same site, requirement for stenting of popliteal artery, presence of proximal vascular prosthesis, an aneurysm of the superficial femoral or popliteal artery. The primary endpoint of the study was in-stent percent mean diameter stenosis measured with quantitative angiography at 6 months. Secondary endpoints included: restenosis rate as measured by angiography and duplex ultrasound; ankle brachial indices; hemodynamic failure; Rutherford classification; pharmacokinetic sampling for Sirolimus; the incidence of procedure or stent-related adverse events; and quality of life. Patient characteristics were similar, except for the fact that 100% of the sirolimus treated vessels were calcified, whereas only 47% of control vessels were calcified ($p=0.002$). Both groups had similar baseline angiographic characteristics. Follow-up was complete in 16 sirolimus lesions and 17 control lesions. Patients treated with sirolimus had a significantly greater mean stent diameter seen at 6 months than the control group (4.95 mm vs 4.31 mm). No occlusion, in-lesion restenosis, or in-stent restenosis was seen in the sirolimus group, compared to one occlusion, four in-lesion restenoses, and three in-lesion stenoses in the control group. These findings were not statistically significant.

Conclusions

Primary stenting for peripheral occlusive disease of the femoropopliteal segment has not yielded better long-term outcomes than balloon angioplasty alone. The initial improvement in technical success seen with stenting is counterbalanced by an increased incidence of neointimal hyperplasia. As such, stenting has been seen primarily as a rescue therapy for failed angioplasty. However, with the advent of sirolimus-eluting stents and their early success in treating obstructing lesions of the superficial femoral artery, stenting may ultimately assume a role as first-line therapy. Further clinical trials with larger groups of patients are warranted.

References

1. Bosch JL, Hunink MG. Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. Radiology 1997; 204(1):87–96.
2. Cejna M, Thurnher S, Illiasch H, et al. PTA versus Palmaz stent placement in femoropopliteal artery obstructions: a multicenter prospective randomized study. J Vasc Interv Radiol 2001; 12(1):23–31.
3. Muradin GS, Bosch JL, Stijnen T, Hunink MG. Balloon dilatation and stent implantation for treatment of femoropopliteal arterial disease: a meta-analysis. Radiology 2001; 221(1):137–145.
4. Poon M, Badimon JJ, Fuster V. Overcoming restenosis with sirolimus: from alphabet soup to clinical reality. Lancet 2002; 16:359(9306):619–622.
5. Klugherz D, Llanos G, Lieuallen W, et al. Twenty-eight-day efficacy and pharmacokinetics of the sirolimus-eluting stent. Coron Artery Dis 2002; 13(3):183–188.
6. Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001; 104(5): 600–605.
7. Morice MC, Serruys PW, Sousa JE, et al. The RAVEL Study Group. A randomized comparison of a Sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346:1773–1780.
8. Oliva VL. The SIRROCCO study — clinical investigation of the sirolimus coated Cordis SMART™ nitinol self-expandable stent for the treatment of obstructive superficial femoral artery disease. Cardiovascular research foundation symposium: enter the drug-eluting stent revolution, Atlanta, GA, March 16, 2002.

Endovascular Treatment of Abdominal Aortic Aneurysms

Peter L. Faries, M.D.[1], Nicholas J. Morrissey, M.D.[2], Victoria J. Teodorescu, M.D.[2],
Larry H. Hollier, M.D.[3], and Michael L. Marin, M.D.[4]

Abstract

Minimally invasive endovascular techniques for the treatment of abdominal aortic aneurysm have significantly reduced its morbidity compared to that following standard surgical repair. Moreover, patients with extensive comorbid medical illnesses, for whom standard operative repair is contraindicated may be successfully treated using endovascular means. The full limitations and indications for use of endovascular grafts have not yet been fully defined. The effectiveness of commercially fabricated devices is currently being evaluated. This article describes the general principles of use for endovascular devices for the repair of abdominal aortic aneurysms and details the features of the devices currently in use, as well as the typical results.

Key Words: Abdominal aortic aneurysm, endovascular, minimally invasive, stent-graft.

Introduction

Rupture of abdominal aortic aneurysms (AAA) results in considerable morbidity and mortality. Significant cost to society is also associated with the rupture and treatment of AAA (1). Estimates of the rate of occurrence of AAA are 60 per 1000 in the general population as documented by epidemiological studies (2), and between 1.8% and 6.6% according to autopsy studies (1). The incidence of AAA increases with age and appears to be increasing in industrialized countries, independent of increased longevity (2–4).

The natural history of AAA has been studied for patients who were unable to undergo surgical repair as well as for patients with AAA prior to the development of surgical treatment. In these studies the rate of aneurysm rupture and death could exceed 60% within 3 years of the initial diagnosis (5). Surgical repair (first report in 1952 [6]) is the first and (so far) the only effective treatment for AAA. Morbidity and mortality rates ranging from 3–5% have been reported for elective standard operative repair in major vascular centers (7). However, these rates increase significantly for patients with significant comorbid medical conditions, particularly coronary artery disease, renal failure and chronic obstructive pulmonary disease. Aneurysm repair surgery is currently performed on approximately 50,000 patients per year.

In the United States, more than 15,000 deaths due to aneurysm rupture occur each year (8). It is estimated that at least 62% of patients who experience rupture of an AAA die prior to reaching the hospital (9). The overall mortality rate for ruptured AAA, including in-hospital deaths, is thought to approach 90% (9–11). In addition to the significant loss of life associated with AAA rupture, there are significant health care costs. Cost reimbursement studies document an average loss to the hospital of approximately $25,000 per patient presenting with a ruptured AAA (12). It is estimated that 2,000 lives and $50 million could be saved annually in the United States alone if aortic aneurysms were repaired prior to rupture (13).

---

[1] Chief of Endovascular Surgery, New York-Presbyterian Hospital and Assistant Professor of Surgery, Weill Cornell Medical School, New York, NY; and [2] Assistant Professor of Surgery and [4] Chief and Professor of Surgery, Division of Vascular Surgery, Department of Surgery, and [3] Chairman and Professor of Surgery, Department of Surgery, Mount Sinai School of Medicine, New York, NY

Address correspondence to Peter L. Faries, M.D., Division of Vascular Surgery, New York-Presbyterian Hospital, Weill Cornell Medical School, 1300 York Avenue, New York, NY 10021; E-mail. plf2001@med.cornell.edu

Origins of Endovascular Abdominal Aortic Aneurysm Repair

The development of endovascular techniques for endovascular treatment of AAA was initiated by Juan C. Parodi, M.D. and his colleagues (14). These techniques use the transfemoral route of delivery of the endovascular device. Parodi's device was created from prosthetic vascular grafts or conduits combined with balloon-expandable stents. Since Parodi's initial report, numerous other endovascular devices have been developed and tested for the treatment of AAA.

Current Indications for Endovascular Repair

Since the selection criteria and indications for the endovascular repair of AAA are constantly evolving, there is no precise agreement on what these criteria should be. During the initial experience with endovascular AAA repair, patients were offered endovascular treatment on a compassionate-need basis. Endovascular grafts were used to treat patients who had aneurysms that were at significant risk for rupture but who could not tolerate standard surgical repair. Endovascular repair remains the most appropriate treatment choice for this category of patient. However, the use of endovascular devices to treat AAAs in patients who would be candidates for open surgical repair has increased significantly. The decision to use endovascular techniques to treat AAA is greatly affected by the anatomical constraints of the device.

Anatomical Selection Criteria

A number of anatomical and technical criteria must be fulfilled if endovascular repair of AAA is to be performed successfully. These criteria include:

- The presence of an undilated segment of aorta distal to the renal ostia that is of sufficient length to allow implantation of the proximal aspect of the endovascular device; this is the proximal neck. The length of normal proximal aorta necessary for device implantation varies according to the specifications of the individual device and ranges from 1.0 – 1.5 cm.

- Severe angulation of the proximal neck may also preclude endovascular treatment. Generally, an angle less than 60° between the suprarenal aorta and the proximal neck is considered excessive, although variation according to the specific device type ultimately determines the maximum acceptable angle.

- If the site selected for distal implantation is the iliac artery, its morphology must be adequate for seating of the distal attachment system of the endovascular device.

- The common and external iliac arteries must be of sufficient caliber to allow passage of the introducer sheath or must be amenable to balloon dilatation to facilitate passage.

- The iliac vessels must demonstrate limited tortuosity.

- Aberrant vessels, particularly an indispensable inferior mesenteric or accessory renal artery, must not be present in the segment of aorta to be excluded from the circulation.

If these criteria are not met, it may not be possible to carry out the procedures because of technical reasons. In addition, some investigators consider a life expectancy of less than 2 years to be a relative contraindication.

Preoperative Assessment

Adequate assessment of the AAA, using radiological evaluation, must be performed to determine the diameter and length of the endovascular device to be used. In general, a screening computed tomographic (CT) scan with intravenous contrast is performed. Ideally, a high-speed, helical scanner is used to obtain images at 3 mm intervals. Three-dimensional reconstruction images may also be obtained. The dimensions of the proximal and distal aortic necks as well as the aneurysm length and composition can be calculated. In addition, the length of the endovascular graft necessary for treatment of the aneurysm may be estimated using three-dimensional reconstruction of the CT.

Angiography with a marker catheter may be used in the assessment of arterial length as well as the adjacent arterial structures. Assessment of the renal and inferior mesenteric arteries, in particular, may be performed. A calibrating catheter with radiopaque markers at 1 cm intervals is used. This catheter allows for the compensation of parallax and magnification, permitting greater accuracy in determining the length of graft necessary for endovascular treatment (15). A wire pull-back technique may also be employed, so that distances can be measured from the movement of the guidewire relative to the end of the angiographic catheter, as the tip of the guidewire is pulled from one anatomical structure to another (16). Arteriography provides invaluable information regarding the presence of aberrant vessels as well as the presence of tortuosity and kinking of the iliac vessels. The precise measurements obtained by arteriography can be used to tailor the endovascular device to the patient's particular requirements.

Deployment of Endovascular Devices

Endovascular AAA repair is most commonly performed in the operating room. This environment is the safest and the best suited for handling potential complications that might be encountered, including iliac artery perforation, damage to the femoral access site, aortic thrombosis and the need to rapidly convert to an open repair. Also, since these procedures involve the introduction of a vascular graft, sterile technique is of the utmost importance; some investigators believe that this is best maintained in the operating room (15).

Prior to surgery the patient is fully prepared and draped in a sterile manner. The endovascular procedure is performed under fluoroscopic guidance, so the operating room should be equipped with advanced fluoroscopic instruments and a radiolucent operating table. A radiopaque-marked backboard or ruler may be placed beneath the patient to provide fluoroscopic reference measurements. Access to the arterial system is obtained either through exposure of the common femoral artery or, if this vessel is inadequate, through a limited retroperitoneal approach to the iliac artery. Once arterial access has been obtained, wire and catheter techniques are employed to place the device.

Following deployment of the endovascular graft, a completion arteriogram is performed. Some centers advocate the use of intravascular ultrasound to assess graft deployment and determine the presence of graft stenosis or kinking. Luminal narrowing, particularly in the iliac limbs of the graft, may be treated by balloon angioplasty and stent placement. Follow-up regimens vary, but usually include serial abdominal CT scans and may include color-flow duplex scanning or magnetic resonance imaging. If an abnormality or change from baseline is detected, arteriography is performed to fully evaluate the status of the graft and the implantation sites, as well as any persistently patent endoleaks or patent aneurysm in side branches.

Commercially Fabricated Endovascular Devices

After the initial success of endovascular stent grafts fabricated by vascular surgeons, commercially fabricated endovascular devices began to be developed. These devices have received considerable clinical exposure, and seven of them are currently either in use or undergoing trials. One device, the Guidant Ancure, has been withdrawn from use after initial approval by the FDA.

1. AneuRx (Medtronic, Inc., Minneapolis, MN);
2. Talent (World Medical, Sunrise, FL);
3. Zenith (Cook Inc., Bloomington, IN);
4. Anaconda (Sulzer Vascutek, Austin, TX);
5. Endologix (Endologix, Irvine, CA);
6. Excluder (W.L. Gore and Associates, Flagstaff, AZ);
7. Quantum (Cordis, Inc./Cordis, Sommerville, NJ).

The Guidant/EVT Ancure Device

The Guidant Ancure stent graft deserves special mention. Originally designed and produced by Endovascular Technologies, the Ancure endograft system was the first stent graft to be produced commercially. Phase I and II clinical trials were completed and the device received FDA approval in 1999 (16). Initial reports found the device to be generally safe and efficacious. (17). However, subsequent review of the data relating to the use of the Ancure graft revealed significant difficulties associated with delivery and deployment of the device. These difficulties resulted in considerable morbidity and in mortality in a significant number of cases. In addition, the Guidant Corporation misrepresented the results on the use of this stent graft to the FDA. As a result, the device has now been withdrawn from use.

The AneuRx Device

A modular, bifurcated, self-expanding stent-graft system was developed by AneuRx (Fig.

1). The modular components consist of a thin-walled, noncrimped, woven polyester graft supported by a nitinol (nickel-titanium alloy) frame. Modular aortic and iliac extenders may also be added. All components are contained in a delivery sheath, which is introduced bilaterally through the femoral vessels.

The results of a nonrandomized, multicenter clinical trial comparing endovascular AAA treatment with the AneuRx device to conventional open repair have been reported (18) (Table). During an 18-month period, 190 patients underwent AAA repair using this device. The operative mortality rate was 2.6%. The overall morbidity rate was 17% with a 12% major morbid event rate, which included myocardial infarction, stroke, renal failure and arrhythmia. Minor morbidities (5%) included wound infection, minor toe embolization, mild femoral neuropathy and an increase in creatinine that did not require treatment. The use of the AneuRx device, when compared with surgical treatment, was found to offer advantages in reducing the rate of major morbidity and length of hospital stay.

The device has received approval from the U.S. FDA, having completed phase I and II trials (18). In the long-term follow-up of those patients, the AneuRx device was found to have an implant success rate of 98% with a perioperative mortality rate of 1.9%. One-year survival was 94% and 3-year survival was 84%. Conversion to conventional repair was required in 2.8% during 4-year follow-up, with AAA rupture occurring in 0.8% and being largely attributable to persistent endoleaks. The incidence of endoleak was 21% at 1 year and 18% at 3 years. Follow-up of these patients continues.

TABLE
Results of Medtronic AneuRx

	%
Implant success	98
30-day mortality	1.9
Perioperative conversion to standard open repair	1.3
Conversion to conventional repair (at 4 years)	2.8
Secondary procedures	8
1-year survival	94
3-year survival	84
Endoleak at 1 year	21
Endoleak at 3 years	18

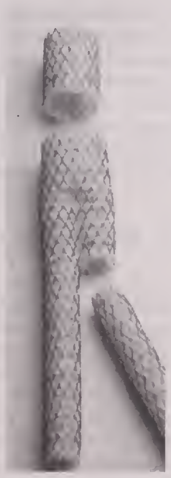

Fig. 1. AneuRx device. The modular design of this graft includes the main bifurcated segment, the contralateral limb, and the proximal and distal extender cuffs.

The Talent Device

The endovascular device developed by Talent has been implanted in more than 13,000 patients worldwide. The Talent graft is used in three configurations: tube/aortic, tapered/Arden-iliac, and bifurcated/aortic-iliac (Fig. 2). It is self-expanding and composed of Dacron with a nitinol frame which supports the graft. Deployment of the device is similar to that of the AneuRx device. First, the aortic component, with one iliac limb, is deployed through a femoral artery cut-down. The second, contralateral iliac limb module is then deployed via the contralateral femoral artery with the proximal aspect seating within the aortic component.

A recent report summarizes the results of an FDA-sponsored investigational device exemption trial for high-risk patients (19). In this trial all patients either had significant comorbid medical conditions or possessed a hostile abdomen. Technical success was achieved in 93% of patients treated with the Talent device. Secondary procedures were required in 8.7%. Conversion to open surgical repair was required in 1% of the cases. The overall 30-day mortality rate was 1.9%. From the reported experience, it was concluded that the Talent endovascular device was suitable for the treatment of AAAs in a significant proportion of patients. It was noted that the proximal aortic fixation device pos-

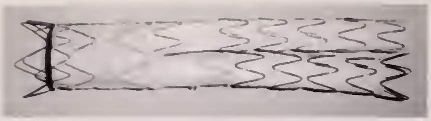

Fig. 2. Bifurcated Talent endovascular graft. The modular Talent graft utilizes a bare stent segment proximally that allows for transrenal fixation.

sesses approximately 1 cm of uncovered nitinol frame proximal to the fabric portion of the device. This uncovered portion permits transrenal fixation of the device, thereby allowing the treatment of AAAs with relatively short proximal necks (19).

The Zenith AAA Endovascular Graft

The Zenith system from Cook is a modular bifurcated device, but is also available in an Arden-iliac configuration. It consists of woven polyester graft material supported throughout its length by self-expanding Z-stents. The introducer tip is tapered to minimize trauma at the arterial insertion site, and there are side holes at the tip to allow angiography when the system is in place. The Zenith stent-graft system has a bare proximal stent that expands radially upon deployment. There are barbs at the top of this bare stent to secure the device to the suprarenal aortic wall. The suprarenal bare stent is deployed after being released by a trigger wire, which holds it in place to avoid premature deployment. This device is currently undergoing clinical trials and is not yet approved for use in the U.S..

The Anaconda System

The Anaconda stent-graft system for aneurysm treatment is a fully modular system made of woven material one third thinner than conventional graft material. The stents are made of nitinol. A unique feature is the proximal ring stent, which is composed of multiple turns of nitinol wire. The hoop strength that results from the radial force of this ring stent allows the proximal end to be anchored to the aortic wall. Because of the saddle configuration of the proximal ring stent, the device can be placed so that the graft is situated at and above the renal ostia while the renal ostia themselves are uncovered. A system of magnets is used to aid in cannulating the main body of the graft in order to position the contralateral limb in place. Because it is a fully modular system, there is theoretically an increased risk of an endoleak developing at the graft junction sites because of the increased number of articulations between pieces. This device is also currently undergoing clinical trials.

Endologix PowerLink System

The Endologix PowerLink system is a one-piece bifurcated graft composed of polytetrafluoroethylene (PTFE). The one-piece design eliminates the risk of endoleaks seen at attachment sites in modular devices. In addition, the frame is composed of a self-expanding non-nitinol wire, which eliminates the need for sutures to hold individual stents in place. The graft is thin-walled PTFE, which may allow for downsizing of the delivery system. This system is currently available for investigational use only.

The Gore Excluder Endoprosthesis

The Excluder stent-graft system is composed of thin-walled PTFE externally supported throughout its length with nitinol stents. It is a modular bifurcated system. The main body is delivered through an 18F sheath, while the contralateral limb is delivered through a 12F sheath (Fig. 3). There are no suture holes in the graft material; thus, the risk for leakage through fabric tears is reduced. There is an external sealing cuff at the proximal end to aid in fixation to the proximal attachment point. A PTFE fiber deployment line is pulled to permit rapid deployment of the device. The release occurs rapidly and without lengthening or shortening of the prosthesis. The Excluder is currently undergoing clinical trials in the United States.

The Quantum Endovascular Device

Transrenal fixation of the proximal aspect of the endovascular graft appears to offer significant advantages for patients with short or angulated proximal necks. In addition, the ability to adjust iliac graft length once an endovascular device has been inserted into the arterial system is necessary to provide optimal aneurysm exclusion. The Quantum endovascular aortic graft is constructed from seamless nitinol hypo-tube stents, which provide the thermal memory properties of the nitinol metal material. The attachment system is equipped with a trans-

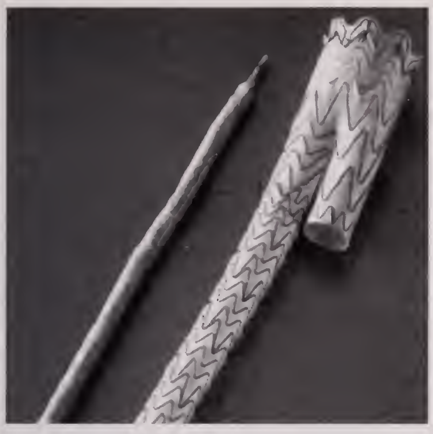

Fig. 3. Bifurcated Gore Excluder. The main body and ipsilateral limb with delivery system (left). Although the modular design is similar to other endografts, the use of PTFE graft material allows for deployment through a smaller delivery system.

renal segment, which optimizes renal artery blood flow while enhancing suprarenal fixation (Fig. 4). Fully integrated, self-deploying barbs engage the aortic wall immediately below the lowest renal artery. This region of the aorta has proven to be least susceptible to progressive dilatation. The aortic body and iliac extender limbs have been designed to achieve *in situ* sizing of the endograft. Once the aortic body of the endograft is deployed, the length of the iliac limbs can be adjusted to provide optimal exclusion of the iliac aneurysmal component, while preserving flow to the internal iliac artery. Modular extenders for aortic and iliac components are also available to further optimize durable aneurysm exclusion.

Summary

Endovascular treatment of AAA has been undergoing evaluation in the clinical setting since 1991. The techniques have been carried out with considerable success at various centers in the United States and abroad. When the AAA is successfully treated endovascularly, a reduction in diameter is frequently observed. Complications including death and technical difficulties relating to device deployment have been encountered. Nevertheless, significant reductions in major morbid events have been observed with endovascular treatment of AAA as compared with standard open surgery. In addition, endovascular devices provide a means of treating patients whose comorbid illnesses make conventional open repair difficult or impossible. Long-term follow-up is only now beginning to be reported for patients treated with endovascular devices, and these initial long-term data appear promising. The eventual patient criteria for the use of endovascular devices

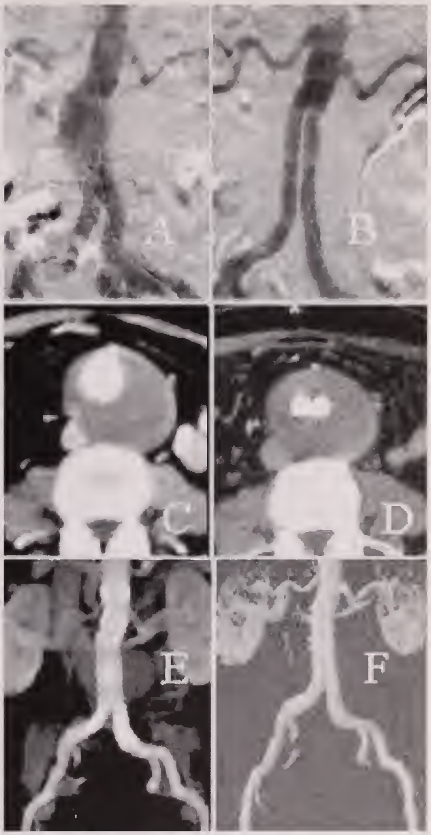

Fig. 4. Teramed Cordis endovascular aneurysm repair. Panels **A and C** are preoperative images of a 72-year-old man with an abdominal aortic aneurysm. Panels **B, D, E and F** are images following the insertion of an endovascular aortic stent graft. The aneurysm is completely excluded in the postoperative angiograms. Panel **E** is a maximum intensity projection done one year after endovascular aortic repair. Panel **F** is a 3-dimensional reconstruction which demonstrates that the aneurysm is excluded.

in the treatment of AAAs will need to be more completely defined as additional clinical experience is gained and the long-term results of prospective, randomized trials are evaluated.

References

1. Reilly JM, Tilson MD. Incidence and etiology of abdominal aortic aneurysms. Surg Clin N Am 1989; 69:705–711.
2. Melton L, Bickerstaff L, Hollier L, et al. Changing incidence of abdominal aortic aneurysms: a population-based study. Am J Epidemiol 1984; 120:379–386.
3. Lilienfeld DE, Grunderson PD, Sprafka J, Vargas C. The epidemiology of abdominal aortic aneurysms: 1. Mortality trends in the United States, 1951 to 1980. Atherosclerosis 1987; 7:637–643.
4. Castleden W, Mercer J. Abdominal aortic aneurysms in Western Australia: descriptive epidemiology and patterns of rupture. Br J Surg 1985; 72:109–112.
5. Moore WS. Endovascular grafting technique. In: Yao JST, Pearce WH, editors. Aneurysms: new findings and treatments. Norwalk (CT): Appleton and Lange; 1995. pp. 333–340.
6. Dubost C, Allary M, Oeconomos N. Resection of aneurysm of abdominal aorta: reestablishment of continuity by preserved human arterial graft, with result after five months. Arch Surg 1952; 64:405–408.
7. Ernst CB. Abdominal aortic aneurysm. N Engl J Med 1993; 328:1167–1172.
8. National Center for Health Statistics. Vital statistics of the United States, 1988. Vol. 2: Mortality. Part A. Washington, DC: Government Printing Office; 1991. DHS Publication no. [PHS] 91-11010.
9. Ingoldby CJ, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. Br J Surg 1986; 73:551–553.
10. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. Br J Surg 1986; 73:101–103.
11. Thomas PR, Stewart RD. Abdominal aortic aneurysm. Br J Surg 1988; 75:733–736.
12. Breckwoldt WL, Mackey WC, O'Donnell TF, Jr. The economic implications of high-risk abdominal aortic aneurysms. J Vasc Surg 1991; 13:798–804.
13. Pasch AR, Ricotta JJ, May AG, et al. Abdominal aortic aneurysm: the case for elective resection. Circulation 1984; 70(3 Pt 2):11–14.
14. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991; 5:491–499.
15. Moore WS. Transfemoral endovascular repair of abdominal aortic aneurysm: feasibility study of the EGS system. In Parodi JC, Veith FJ, Marin ML, editors. Endovascular grafting techniques. St. Louis (MO): Quality Medical Publishing; 1995. pp. 234–256.
16. Moore WS. The EVT tube and bifurcated endograft systems: technical considerations and clinical summary. EVT Investigators. J Endovasc Surg 1997; 4:182–194.
17. Jacobowitz GR, Lee AM, Riles TS. Immediate and late explantation of endovascular aortic grafts: the Endovascular Technologies experience. J Vasc Surg 1999; 29:309–316.
18. Zarins CK, White RA, Schwarten D, et al. AneuRx stent graft versus open surgical repair of abdominal aortic aneurysms: multicenter prospective clinical trial. J Vasc Surg 1999; 29:292–308.
19. Faries PL, Brener BJ, Connelly TL, et al. A multicenter experience with the Talent endovascular graft for the treatment of abdominal aortic aneurysms. J Vasc Surg 2002; 35:1123-1128.

List of Journal Reviewers in 2003

Each year The Journal relies on its reviewers to actively participate in the selection of those manuscripts considered to be worthwhile, timely, interesting, and factual. The Journal staff thanks the following reviewers for their time and intellectual effort.

Louis M. Aledort
Edward J. Bottone
Constantin A. Bona
A. Philip Chahinian
Liane Deligdisch
Marie De Sancho
Frederick Friedman
James L. Gladstone
Adrian Greenstein
Richard S. Haber
Shirish Huprikar
Stanley Jordan
Alex Kirschenbaum
Leslie A. Kuhn
Carin I. Lamm
Nathan Levin
Alice Levine
Lloyd F. Mayer
Thomas M. Moran
Ira S. Nash
David M. Nierman
Daniel P. Perl
Elliot J. Rayfield
Fred Rosner
Harry Spiera
Alvin S. Teirstein
Jaime Uribarri
Joseph Vassalotti

Statement of Ownership, Management and Circulation filed with the U.S. Postal Service. Average number of copies each issue for the 12-month period ending September 30, 2003: 15a. net press run, 1667; 15b1. paid and/or requested (subscriptions, by mail, outside county), 248; 15b2. paid and/or requested (subscriptions, by mail, inside county), 0; 15b3. paid and/or requested (paid distribution, by carriers or other means), 1343; 15b4. paid and/or requested (other classes, by mail), 0; 15c. total paid and/or requested, 1591; 15d1. free distribution by mail (outside county), 0; 15d2. free distribution by mail (inside county), 0; 15d3. free distribution by mail (other classes), 0; 15e. free distribution by carriers or other means, 0; 15f. total free distribution, 0; 15g. total distribution, 1591; 15h. copies not distributed, 76; 15i. total number of copies, 1667; 15j. percent paid and/or requested, 100%. Number of copies of issue published nearest to filing date (September 2003): 15a. net press run, 1600; 15b1. paid and/or requested (subscriptions, by mail, outside county), 238; 15b2. paid and/or requested (subscriptions, by mail, inside county), 0; 15b3. paid and/or requested (paid distribution, by carriers or other means), 1252; 15b4. paid and/or requested (other classes, by mail), 0; 15c. total paid and/or requested, 1490; 15d1. free distribution by mail (outside county), 0; 15d2. free distribution by mail (inside county), 0; 15d3. free distribution by mail (other classes), 0; 15e. free distribution by carriers or other means, 0; 15f. total free distribution, 0; 15g. total distribution, 1490; 15h. copies not distributed, 110; 15i. total number of copies, 1600; 15j. percent paid and/or requested, 100%.

Author, Subject, Title Index to Volume 70

Abdominal aortic aneurysm: 70(6):420–426
Abdominal complications: 70(2):130–132
Abuse: 70(2):69–74
Acute abdomen: 70(2):130–132
Acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries, an: an undescribed disease, E Moschcowitz: 70(5):353–355
Addis MD, Inabnet WB, Minimally invasive endocrine surgery: 70(5):333–337
Adrenalectomy: 70(5):333–337
Advance directives: 70(2):85–92
Advanced glycation end product: 70(4):232–241
Advances in angiography and their impact on endovascular therapy, HA Mitty: 70(6):359–363
Aged: 70(2):75–84
Agich GJ, Risks, benefits, and quality of life: 70(3):141–147
Aging: 70(1):3–22; 70(2):69–74
Aguero-Rosenfeld ME, Laboratory aspects of tick-bome diseases: Lyme, human granulocytic ehrlichiosis and babesiosis: 70(3):197–206
Alexis JD, Pyo RT, Chereshnev I, Immunologic factors in transplant arteriopathy: insight from animal models: 70(3):191–196
Allergy to antibiotics: 70(2):113–125
Altchek A, Uterus transplantation: 70(3):154–162
Alzheimer's disease: 70(1):45–53
Amnioinfusion: 70(2):126–129
Anger: 70(2):101–112
Angiography: 70(6):357–358; 70(6):359–363; 70(6):367–374
Angiotensin-converting enzyme inhibition: 70(4):225–231
Announcement of 2002 Awards: 70(5):288
Antagonistic pleiotropy: 70(1):3–22
Antiestrogens: 70(4):215–224
Aortic aneurysm: 70(6):364–366
Aortic arch vessels: 70(6):401–409
Arteriopathy: 70(3):191–196
Arthritis: 70(1):23–26
Asthma: 70(3):185–190; 70(4):215–224
Apoptosis: 70(4):242–250
Aufses AH Jr., Physicians and scientists for your grandchildren: 70(5):289–292
Autoantibody: 70(4):242–250

Babesiosis: 70(3):197–206
Bach N, Odin JA, Primary biliary cirrhosis: a Mount Sinai perspective: 70(4):242–250
Bacterial pathogens: 70(2):126–129
Banerjee A, Talreja A, Sonnenblick EH, LeJemtel TH, Evolving rationale for angiotensin-converting enzyme inhibition in chronic heart failure: 70(4):225–231
Baran DA: see Galin I
Basaria S, Krop JS, Braga-Basaria M, A rare cause of pituitary stalk enlargement and panhypopituitarism: 70(4):265–267
B-cell: 70(2):133–138
Behavioral cardiology: 70(2):101–112
Behavioral cardiology — has its time finally arrived? T Pickering, L Clemow, K Davidson, W Gerin: 70(2):101–112
Berkowitz RL: see Lembet A
Biology of aging, the, BR Troen: 70(1):3–22
Blood transfusion: 70(5):310–325
Bone marrow: 70(2):133–138
Borrelia burgdorferi: 70(3):207–213
Bottone EJ: see Lembet A
Braga-Basaria M: see Basaria S
Brain-derived neurotrophic factor (BDNF): 70(2):93–100
Burrows L: see Moros DA

Caldwell MC: see Chow CC
Cancer: 70(1):3–22
Candidate selection criteria for living donor liver transplantation, M Schwartz: 70(3):171–173
Capello: see Paris BEC
Caracta CF, Gender differences in pulmonary disease: 70(4):215–224
Cardiac surgery: 70(5):310–325
Cardiothoracic surgery at The Mount Sinai Hospital, RS Litwak: 70(5):310–325
Cardiac surgery, history of: 70(5):310–325
Cardiovascular disease in women, WL Duvall: 70(5):293–305
Carney MT, Kahan FS, Paris BEC, Elder abuse: is every bruise a sign of abuse?: 70(2):69–74
Carroccio A: see Ellozy SH
Case study: 70(4):251–264
Castor T: see McParland E
Catheterization: 70(6):357–358
Catheters: 70(6):386–392
Celiac disease: 70(4):242–250
Cellular: 70(1):3–22
Cerebrovascular disorders: 70(1):27–37
Chemokine: 70(3):191–196
Chereshnev I: see Alexis JD
Chichin E: see McParland E
Cholangiocytes: 70(4):242–250
Chorioamnionitis: 70(2):126–129
Chow CC, Evans AS Jr., Noonan-Toly CM, White D, Johnson GS, Marks SJ, Caldwell MC, Hayes EB, Lyme disease trends — Dutchess County, New York, 1992–2000: 70(3):207–213
Chronic heart failure: 70(4):225–231
Cigarette smoking: 70(4):215–224
Classics in Medicine: Intravenous urography by means of the sodium salt of 5-iodo-2-pyridon-N-acetic acid, M Swick: 70(4):269–279; Intravenous urography (Swick method), L Jaches: 70(4):280–287; Acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries, an: an undescribed disease, E Moschcowitz: 70(5):353–355
Clemow L: see Pickering T
Clinical trials: 70(1):27–37
Coated stents: 70(6):386–392
Commencement Address — 2003: Physicians and scientists for your grandchildren, AH Aufses Jr.: 70(5):289–292
Congestive heart failure: 70(4):251–264
Congestive heart failure: guidelines for the primary care physician, I Galin, DA Baran: 70(4):251–264
Controversies in differentiating thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, NT Shah, JH Rand: 70(5):344–352
COPD: 70(4):215–224
Coronary artery disease: 70(5):293–305

Coronary heart disease: 70(2):101–112; 70(5):293–305
Croft LB: see Henzlova MJ
CT angiography: 70(6):367–374
Cytokine: 70(3):191–196

Davidson K: see Pickering T
Dean's Lecture: Neurotrophins, growth-factor-regulated genes and the control of energy balance, SRJ Salton: 70(2):93–100
Dementia: 70(1):45–53
Depression: 70(1):38–44; 70(2):101–112
Detection of abuse: 70(1):62–68
Devices and techniques for endovascular surgery: catheters, stents, coated stents, and stented grafts, L Pukin: 70(6):386–392
Diabetes: 70(2):93–100
Diagnosis: 70(1):38–44
Diet: 70(2):101–112
Drug allergy: 70(2):113–125
Drug-eluting stents: 70(6):417–419
Drug-eluting stents in peripheral vascular disease: eliminating restenosis, SH Ellozy, A Carroccio: 70(6):417–419
Drug hypersensitivity: 70(2):113–125
Drug rashes: 70(2):113–125
Dugué M, Neugroschl J, Sewell M, Marin D, Review of dementia: 70(1):45–53
Duplex ultrasonography: 70(6):364–366
Duplex ultrasonography and its impact on providing endograft surveillance, VJ Teodorescu, NJ Morrissey, PL JW Olin: 70(6):364–366
Duvall WL, Cardiovascular disease in women: 70(5):293–305

ECG: 70(5):306–309
Editorial: Classics in Medicine: Acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries, an: an undescribed disease, E Moschcowitz: 70(5):353–355
Editors' Note: Imaging in medicine, S Kupfer: 70(4):268
Ehrlichiosis: 70(3):197–206
Ejection fraction: 70(5):306–309
Elder: 70(2):75–84
Elder abuse: 70(1):62–68; 70(2):69–74
Elder abuse: is every bruise a sign of abuse? MT Carney, FS Kahan, BEC Paris: 70(2):69–74
Elder mistreatment: 70(1):62–68
Elder neglect: 70(1):62–68
Elderly: 70(1):23–26; 70(1):27–37; 70(1):38–44; 70(1):45–53; 70(2):69–74
Electrocardiogram as a predictor of left ventricular systolic function, the: correlation with gated SPECT imaging, MJ Henzlova, LB Croft: 70(5):306–309
Elkind MSV, Stroke in the elderly: 70(1):27–37
Ellozy SH, Carroccio A, Drug-eluting stents in peripheral vascular disease: eliminating restenosis: 70(6):417–419
Emergency: 70(2):75–84
Emergency contraception: 70(5):338–343
Emergency department: 70(2):75–84
Emergency prophylaxis following needle-stick injuries and sexual exposures: results from a survey comparing New York emergency department practitioners with their national colleagues, RC Merchant, R Keshavarz: 70(5):338–343
Endograft repair: 70(6):364–366
Endovascular: 70(6):410–416; 70(6):420–426
Endovascular devices: 70(6):386–392
Endovascular repair of diffuse atherosclerotic occlusive disease using stented grafts, EC Gravereaux, ML Marin: 70(6):410–416
Endovascular surgery: 70(6):386–392
Endovascular techniques: 70(6):401–409
Endovascular therapy: 70(6):359–363; 70(6):367–374; 70(6):393–400
Endovascular therapy for atherosclerotic occlusion and stenosis from the infrarenal aorta to the infrapopliteal arteries, FS Nowakowski, HJ Freeman: 70(6):393–400
Endovascular treatment of abdominal aortic aneurysms, PL Faries, NJ Morrissey, VJ Teodorescu, LH Hollier, ML Marin: 70(6):420–426
Epidemiology: 70(1):27–37; 70(4):215–224; 70(5):293–305
Escherichia coli: 70(2):126–129
Estrogens: 70(4):215–224
Ethical consideration: 70(3):163–165
Ethical limitations: 70(3):174–177
Ethical limits of transplantation, Moros DA, Rhodes R, Burrows L, guest editors: 70(3):139–184
Ethics: 70(3):141–147; 70(3):148–153; 70(3):154–162; 70(3):166–170; 70(3):171–173
Evans AS Jr.: see Chow CC
Evolving rationale for angiotensin-converting enzyme inhibition in chronic heart failure, A Banerjee, A Talreja, EH Sonnenblick, TH LeJemtel: 70(4):225–231
Exercise: 70(2):101–112

Falk A: see Keshava SN
Faries PL, Morrissey N, Teodorescu V, Hollier LH, Marin ML, Endovascular treatment of abdominal aortic aneurysms: 70(6):420–426
Femoral arteries: 70(6):393–400
Frailty: 70(2):69–74
Freeman HJ: see Nowakowski FS
Fruchtman S, Stem cell transplantation: 70(3):166–170
Fuster V: see Marin ML

Gaddipati S: see Lembet A
Galin I, Baran DA, Congestive heart failure: guidelines for the primary care physician: 70(4):251–264
Gated SPECT: 70(5):306–309
Genden EM, Urken ML, Laryngeal and tracheal transplantation: ethical limitations: 70(3):163–165
Gender differences in pulmonary disease, CF Caracta: 70(4):215–224
Genetics: 70(4):242–250
Geriatric: 70(2):75–84
Geriatrics: Part 1: BEC Paris, CF Capello, guest editors, 70(1):1–68; Part 2: BEC Paris, CF Capello, guest editors, 70(2):69–92
Gerin W: see Pickering T
Glycoxidation: 70(4):232–241
Glycoxidation: the menace of diabetes and aging, H Vlassara, MR Palace: 70(4):232–241
Goldman JP, New techniques and applications for magnetic resonance angiography: 70(6):375–385
Gout: 70(1):23–26
Grand Rounds: Behavioral cardiology — has its time finally arrived? T Pickering, L Clemow, K Davidson, W Gerin: 70(2):101–112; Hypersensitivity reactions to drugs: evaluation and management, GM Shepherd: 70(2):113–125; Immunologic factors in transplant arteriopathy: insight from animal models, JD Alexis, RT Pyo, I Chereshnev: 70(3):191–196; Laboratory aspects of tick-bome diseases: Lyme, human granulocytic ehrlichiosis and babesiosis, ME Aguero-Rosenfeld: 70(3):197–206; Severe asthma: epidemiology, pathophysiology and treatment, S Wenzel: 70(3):185–190; Gender differences in pulmonary disease, CF Caracta: 70(4):215–224; Evolving rationale for angiotensin-converting enzyme inhibition in chronic heart failure, A Banerjee, A Talreja, EH Sonnenblick, TH LeJemtel: 70(4):225–231; Glycoxidation: the menace of diabetes and aging, H Vlassara, , MR Palace: 70(4):232–241; Primary biliary cirrhosis: a Mount Sinai perspective, N Bach, JA Odin: 70(4):242–250; Cardiovascular disease in women, WL Duvall: 70(5):293–305; Electrocardiogram as a predictor of left ventricular systolic function, the: correlation with gated SPECT imaging, MJ Henzlova, LB Croft: 70(5):306–309
Gravereaux EC, Marin ML, Endovascular repair of diffuse atherosclerotic occlusive disease using stented grafts: 70(6):410–416
Grigoriadis KD: see Sakorafas GH
Group B Streptococcus: 70(2):126–129

GSPECT: 70(5):306–309
Guidelines: 70(4):251–264

Hand: 70(3):148–153
Hand transplant: 70(3):148–153
Hand transplantation: current status, MR Hausman, J Masters, A Panozzo: 70(3):148–153
Hausman MR, Masters J, Panozzo A, Hand transplantation: current status: 70(3):148–153
Hayes EB: see Chow CC
Heart failure: 70(4):251–264
Hemolytic uremic syndrome: 70(5):344–352
Henzlova MJ, Croft LB, Electrocardiogram as a predictor of left ventricular systolic function, the: correlation with gated SPECT imaging: 70(5):306–309
Hepatitis B prophylaxis: 70(5):338–343
History of cardiothoracic surgery: 70(5):310–325
History of thoracic surgery: 70(5):326–332
History of thoracic surgery at Mount Sinai, the, PA Kirschner: 70(5):326–332
HIV post-exposure prophylaxis: 70(5):338–343
Hollier LH: see Faries PL; see Marin ML
Holzman IR: see Lembet A
Hormone replacement therapy: 70(5):293–305
Hypersensitivity reactions to drugs: evaluation and management, GM Shepherd: 70(2):113–125
Hypersensitivity to beta-lactam antibiotics: 70(2):113–125
Hypersensitivity to sulfa drugs: 70(2):113–125
Hypothalamus: 70(2):93–100
Hypothermia: 70(5):310–325

Iliac arteries: 70(6):393–400; 70(6):410–416
Imaging in medicine, S Kupfer: 70(4):268
Immune system: 70(3):191–196
Immunologic factors in transplant arteriopathy: insight from animal models, JD Alexis, RT Pyo, I Chereshnev: 70(3):191–196
Impact of CT angiography on endovascular therapy, RA Lookstein: 70(6):367–374
Inabnet WB: see Addis MD
Incidence: 70(3):207–213
Incontinence: 70(1):54–61
Inflammation: 70(3):185–190
Inflammatory arthritis in the elderly, LD Kerr: 70(1):23–26
Infrarenal aorta: 70(6):393–400
Intimal proliferation: 70(3):191–196
Intra-amniotic infection: 70(2):126–129
Intratracheal anesthesia: 70(5):310–325
Intravenous urography (Swick method), L Jaches: 70(4):280–287
Intravenous urography by means of the sodium salt of 5-iodo-2-pyridon-N-acetic acid, M Swick: 70(4):269–279
Introduction: Ethical limits of transplantation, DA Moros, R Rhodes, L Burrows: 70(3):139–140
Introduction: Geriatrics, BEC Paris, CF Capello: 70(1):1–2
Introduction: Minimally invasive vascular surgery, ML Marin, HA Mitty, LH Hollier, V Fuster: 70(6):357–358

Jaches L, Intravenous urography (Swick method): 70(4):280–287
Jehovah's Witnesses: 70(5):310–325
Johnson GS: see Chow CC

Kahan FS: see Carney MT
Kahan FS, Paris BEC, Why elder abuse continues to elude the health care system: 70(1):62–68
Kerr LD, Inflammatory arthritis in the elderly: 70(1):23–26
Keshava SN, Falk A, Revascularization of aortic arch branches and visceral arteries using minimally invasive endovascular techniques: 70(6):401–409
Keshavarz R: see Merchant RC
Kirschner PA, History of thoracic surgery at Mount Sinai, the: 70(5):326–332
Klausner AP, Vapnek JM, Urinary incontinence in the geriatric population: 70(1):54–61
Krop JS: see Basaria S
Kupfer S, Editors' Note: Imaging in medicine: 70(4):268

Laboratory aspects of tick-borne diseases: Lyme, human granulocytic ehrlichiosis and babesiosis, ME Aguero-Rosenfeld: 70(3):197–206
Laparoscopy: 70(5):333–337
Laryngeal and tracheal transplantation: ethical limitations, EM Genden, ML Urken: 70(3):163–165
Laryngeal transplantation: 70(3):163–165
Left ventricular remodeling: 70(4):225–231
LeJemtel TH: see Banerjee A
Lembet A, Gaddipati S, Holzman IR, Berkowitz RL, Bottone EJ, Meconium enhances the growth of perinatal bacterial pathogens: 70(2):126–129
Leptin: 70(2):93–100
Lifespan: 70(1):3–22
Life-sustaining treatment: 70(2):85–92
Likourezos A: see McParland E
Litwak RS, Cardiothoracic surgery at The Mount Sinai Hospital: 70(5):310–325
Liver transplantation: 70(3):171–173
Living donor candidacy: 70(3):171–173
Living organ donor: 70(3):174–177
Lookstein RA, Impact of CT angiography on endovascular therapy: 70(6):367–374
Lung cancer: 70(2):130–132; 70(4):215–224
Lyme disease: 70(3):197–206; 70(3):207–213
Lyme disease trends — Dutchess County, New York, 1992–2000, CC Chow, AS Evans Jr., CM Noonan-Toly, D White, GS Johnson, SJ Marks, MC Caldwell, EB Hayes: 70(3):207–213
Lymphoma: 70(2):133–138; 70(4):265–267

Macroangiopathy: 70(4):232–241
Magnetic resonance angiography: 70(6):375–385
Marin D: see Dugué M
Marin ML: see Faries PL; see Gravereaux EC
Marin ML, Mitty HA, Hollier L, Fuster V, Guest Editors, Minimally invasive vascular surgery: the evolution of endovascular therapy, Part 1: 70(6):357–426
Marin ML, Mitty HA, Hollier LH, Fuster V, Introduction: Minimally invasive vascular surgery: 70(6):357–358
Marks SJ: see Chow CC
Masters J: see Hausman MR
McParland E, Likourezos A, Chichin E, Castor T, Paris BEC, stability of preferences regarding life-sustaining treatment: a two-year prospective study of nursing home residents: 70(2):85–92
Mechanisms of drug allergy: 70(2):113–125
Meconium: 70(2):126–129
Meconium enhances the growth of perinatal bacterial pathogens, A Lembet, S Gaddipati, IR Holzman, RL Berkowitz, EJ Bottone: 70(2):126–129
Merchant RC, Keshavarz R, Emergency prophylaxis following needlestick injuries and sexual exposures: results from a survey comparing New York emergency department practitioners with their national colleagues: 70(5):338–343
Mesenteric arteries: 70(6):401–409
Metastasis: 70(2):130–132
Methotrexate: 70(4):242–250
Microangiopathy: 70(4):232–241
Minimally invasive: 70(6):367–374; 70(6):393–400; 70(6):410–416; 70(6):420–426
Minimally invasive endocrine surgery, MD Addis, WB Inabnet: 70(5):333–337

Minimally invasive endoscopy: 70(5):333–337
Minimally invasive techniques: 70(6):401–409
Minimally invasive vascular surgery: 70(6):357–358
Minimally invasive vascular surgery: the evolution of endovascular therapy, Part 1, ML Marin, Mitty HA, L Hollier, V Fuster, guest editors: 70(6):357–426
Mistreatment: 70(2):69–74
Mitty HA: see Marin ML
Mitty HA, Advances in angiography and their impact on endovascular therapy: 70(6):359–363
Moros DA, Rhodes R, Burrows L, guest editors Ethical limits of transplantation: 70(3):139–184
Moros DA, Rhodes R, Burrows L, Introduction: Ethical limits of transplantation: 70(3):139–140
Morrissey NJ: see Faries PL; see Teodorescu VJ
Mortality: 70(1):3–22
Moschcowitz E, Acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries, an: an undescribed disease: 70(5):353–355
Mount Sinai Hospital, The: 70(5):326–332
Mycobacteria: 70(4):215–224

Needle-stick injuries: 70(5):338–343
Neglect: 70(2):69–74
Neonatal sepsis: 70(2):126–129
Nerve growth factor (NGF): 70(2):93–100
Neugroschl J: see Dugué M
Neurotrophin: 70(2):93–100
Neurotrophins, growth-factor-regulated genes and the control of energy balance, SRJ Salton: 70(2):93–100
New techniques and applications for magnetic resonance angiography, JP Goldman: 70(6):375–385
Non-Hodgkin's: 70(2):133–138
Noonan-Toly CM: see Chow CC
Nowakowski FS, Freeman HJ, Endovascular therapy for atherosclerotic occlusion and stenosis from the infrarenal aorta to the infrapopliteal arteries: 70(6):393–400

Obesity: 70(2):93–100
Odin JA: see Bach N
Organ transplantation: 70(3):141–147; 70(3):174–177
Olin JW: see Teodorescu VJ
Overview: depression in the elderly, M Serby, M Yu: 70(1):38–44
Overview of geriatric emergencies, BK Richardson: 70(2):75–84
Oxidative stress: 70(4):232–241

Pacemaker implantation: 70(5):310–325
Palace MR: see Vlassara H
Panel Discussion: Ethics: Ethical limits of transplantation: 70(3):178–184
Panhypopituitarism: 70(4):265–267
Panozzo A: see Hausman MR
Parathyroidectomy: 70(5):333–337
Paris BEC: see Carney MT; see Kahan FS; see McParland E
Paris BEC, Capello CF, Introduction: Geriatrics: 70(1):1–2
Pavlakis G: see Sakorafas GH
PC12: 70(2):93–100
Percutaneous angioplasty: 70(6):357–358
Peripheral artery occlusive disease: 70(6):417–419
Peripheral vascular disease: 70(6):393–400; 70(6):410–416
Phenotypes: 70(3):185–190
Physicians and scientists for your grandchildren, AH Aufses Jr.: 70(5):289–292
Physiology: 70(3):185–190
Pickering T, Clemow L, Davidson K, Gerin W, Behavioral cardiology — has its time finally arrived?: 70(2):101–112
Popliteal arteries: 70(6):393–400
Post-exposure prophylaxis: 70(5):338–343
Prevention: 70(5):293–305
Primary biliary cirrhosis: 70(4):242–250
Primary biliary cirrhosis: a Mount Sinai perspective, N Bach, JA Odin: 70(4):242–250
Primary bone marrow b-cell lymphoma: report of four cases, JA Strauchen: 70(2):133–138
Prolapse uterus utilization: 70(3):154–162
Protein oxidation: 70(4):242–250
Pukin L, Devices and techniques for endovascular surgery: catheters, stents, coated stents, and stented grafts: 70(6):386–392
Pyo RT: see Alexis JD
Pyruvate dehydrogenase: 70(4):242–250

Quality of life surgery: 70(3):154–162

Rare cause of pituitary stalk enlargement and panhypopituitarism, a, S Basaria, JS Krop, M Braga-Basaria: 70(4):265–267
Remodeling: 70(3):185–190
Renal arteries: 70(6):401–409
Restenosis: 70(6):417–419
Revascularization of aortic arch branches and visceral arteries using minimally invasive endovascular techniques, SN Keshava, A Falk: 70(6):401–409
Review of dementia, M Dugué, J Neugroschl, M Sewell, D Marin: 70(1):45–53
Reviewers, list of: 70(6):427
Rheumatoid arthritis: 70(1):23–26
Rhodes R: see Moros DA
Rhodes R, Trust and trustworthiness in organ transplantation: Good Samaritan and emotionally related living donors: 70(3):174–177
Richardson BK, Overview of geriatric emergencies: 70(2):75–84
Risk factors: 70(5):293–305
Risks, benefits, and quality of life, GJ Agich: 70(3):141–147
Rumination: 70(2):101–112

Sakorafas GH, Pavlakis G, Grigoriadis KD, Small bowel perforation secondary to metastatic lung cancer: a case report and review of the literature: 70(2):130–132
Salton SRJ, Neurotrophins, growth-factor-regulated genes and the control of energy balance: 70(2):93–100
Schwartz M, Candidate selection criteria for living donor liver transplantation: 70(3):171–173
Senescence: 70(1):3–22
Serby M, Yu M, Overview: depression in the elderly: 70(1):38–44
Severe asthma: epidemiology, pathophysiology and treatment, S Wenzel: 70(3):185–190
Sewell M: see Dugué M
Sex hormones: 70(4):215–224
Sexual assault: 70(5):338–343
Shah NT, Rand JH, Controversies in differentiating thrombotic thrombocytopenic purpura and hemolytic uremic syndrome: 70(5):344–352
Shepherd GM, Hypersensitivity reactions to drugs: evaluation and management: 70(2):113–125
Signs and symptoms of drug hypersensitivity: 70(2):113–125
Small bowel perforation: 70(2):130–132
Small bowel perforation secondary to metastatic lung cancer: a case report and review of the literature, GH Sakorafas, G Pavlakis, KD Grigoriadis: 70(2):130–132
Smoking: 70(2):101–112
Sonnenblick EH: see Banerjee A
Stability of decisions: 70(2):85–92
Stability of preferences regarding life-sustaining treatment: a two-year prospective study of nursing home residents, E McParland, A Likourezos, E Chichin, T Castor, BEC Paris: 70(2):85–92
Stem cell: 70(3):166–170
Stem cell transplantation, S Fruchtman: 70(3):166–170
Stent-graft: 70(6):410–416; 70(6):420–426

Stented grafts: 70(6):386–392
Stents: 70(6):386–392
Strauchen JA, Primary bone marrow b-cell lymphoma: report of four cases: 70(2):133–138
Stress: 70(2):101–112
Stroke: 70(1):27–37
Stroke in the elderly, MSV Elkind: 70(1):27–37
Superficial femoral artery: 70(6):410–416
Surgery: 70(3):163–165
Surveillance: 70(3):207–213
Swick M, Intravenous urography by means of the sodium salt of 5-iodo-2-pyridon-N-acetic acid: 70(4):269–279

Talreja A: see Banerjee A
Teodorescu VJ: see Faries PL
Teodorescu VJ, Morrissey NJ, Olin JW, Duplex ultrasonography and its impact on providing endograft surveillance: 70(6):364–366
Theme Issues: Geriatrics: Part 1: 70(1):1–68; Geriatrics: Part 2: 70(2):69–92; Ethical limits of transplantation: 70(3):139–184; Minimally invasive vascular surgery: the evolution of endovascular therapy, Part 1: 70(6):357–426
Thoracic surgery: 70(5):326–332
Thoracic surgery, history of: 70(5):326–332
Thrombotic thrombocytopenic purpura: 70(5):344–352
Thyroidectomy: 70(5):333–337
Tick-borne diseases: 70(3):197–206
Transplant: 70(3):148–153; 70(3):166–170
Transplantation: 70(3):191–196
Treatment: 70(1):38–44; 70(3):185–190; 70(4):251–264
Troen BR, The biology of aging: 70(1):3–22
Trust: 70(3):174–177
Trust and trustworthiness in organ transplantation: Good Samaritan and emotionally related living donors, R Rhodes: 70(3):174–177

Urinary incontinence in the geriatric population, AP Klausner, JM Vapnek: 70(1):54–61
Urken ML: see Genden EM
Uterus transplantation: 70(3):154–162
Uterus transplantation, A Altchek: 70(3):154–162

Vapnek JM: see Klausner AP
Vascular imaging: 70(6):367–374
Vascular protection: 70(4):225–231
Vascular surgery: 70(6):357–358; 70(6):393–400
VGF: 70(2):93–100
Visceral arteries: 70(6):401–409
Vlassara H, Palace MR, Glycoxidation: the menace of diabetes and aging: 70(4):232–241
Voiding dysfunction: 70(1):54–61

Wenzel S, Severe asthma: epidemiology, pathophysiology and treatment: 70(3):185–190
White D: see Chow CC
Why elder abuse continues to elude the health care system, FS Kahan, BEC Paris: 70(1):62–68
Women: 70(4):215–224; 70(5):293–305

Yu M: see Serby M

Required Form for Authors

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal*.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

4. US Federal Employees

I was an employee of the US government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

	Author(s) Signature	Date		Author(s) Signature	Date
1st			4th		
2nd			5th		
3rd			6th		

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

09/2002

THE
MOUNT SINAI JOURNAL
OF MEDICINE

3 4805 07482702
LEVY LIBRARY, MT. SINAI SCHOOL OF MEDICINE

Forthcoming: Grand Rounds

A Review of Heart Failure Treatment
Gordon H. Guyatt and P.J. Devereaux
McMaster University
Hamilton, Ontario, Canada

Renal Artery Disease: Diagnosis and Management
Jeffrey W. Olin
Mount Sinai School of Medicine

The Multidisciplinary Approach to Hemodialysis Vascular Access at The Mount Sinai Hospital
Joseph A. Vassalotti, Abigail Falk,
Victoria Teodorescu,
and Jaime Uribarri
Mount Sinai School of Medicine

Theme Issues

Ethics 2001 — Medicine, Money and Morals
Rosamond Rhodes and Daniel A. Moros, Editors

Available now:

Methadone Symposium – Part 1:2000
Volume 67: Numbers 5 & 6. 125 pages, $40.00

Methadone Symposium – Part 2:2001
Volume 68: Number 1. 78 pages, $25.00

Issues in Medical Ethics — Understanding Professionalism and Its Implications for Medical Education
Volume 69: Number 6. 71 pages, $25.00

Visit our web page — http://www.mssm.edu/msjournal

MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

LEVY LIBRARY, MT. SINAI SCHOOL OF MEDICINE
3 4805 0748446 8